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A Comprehensive Approach to Urticaria: From Clinical Presentation to Modern Biological Treatments Through Pathogenesis

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Abstract

Urticaria is characterized by the cutaneous presence of wheals (hives), angioedema or both. Acute and chronic urticaria are distinguished based on a duration of less or more than 6 weeks. Chronic urticaria can be further classified into a spontaneous form and several inducible types triggered by specific external stimuli. Lifetime prevalence of urticaria may be up to 20%, with the acute form being way more common than the chronic one. Exacerbating factors (e.g. infections, drugs, food) and immune system alterations have been investigated as main triggers of mast cell activation, which in turn leads to increased vascular permeability and extravasation of inflammatory cells. While diagnostic workup is focused upon history taking, several emerging biomarkers correlate with severity and/or prognosis of the disease and can be necessary to differentiate chronic spontaneous urticaria from other disorders, such as vasculitis and autoinflammatory diseases. Treatment of acute urticaria is based upon H1 antihistamines and short courses of steroids. While H1 antihistamines are also used in chronic spontaneous urticaria, omalizumab is the standard of care in patients who are unresponsive to these. Recently, several new drugs have entered clinical trials to offer a therapeutic possibility for patients unresponsive to omalizumab. Numerous target molecules, such as mediators of mast cells activation, are under investigation. Amongst these, new anti-IgE therapies and possibly IL-5 pathway blockade seem to have reached enough data to move to advanced clinical trials.

Keywords

Acute urticaria · Angioedema · Biologics · Biomarkers · Chronic spontaneous urticaria · Ligelizumab · Mast cells · Omalizumab · Urticaria · Vasculitis

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Abbreviations

AAC	area above the curve
ACEi	Angiotensin converting enzyme inhibitors
ANA	anti-nuclear antibodies
AOSD	Adult onset Still's disease
ASST	autologous serum skin test
AU	Acute urticaria
BHRA	basophil histamine release assay
BTK	Bruton's tyrosine kinase
C5aR	Complement 5a receptor
CAPS	Cryopirin-associated periodic syndromes
CIndU	Chronic Inducible Urticaria
COX-1	cyclooxygenase 1
CRP	c-reactive protein
CRTH2	chemoattractant receptor homologous molecule expressed on the Th2 cell
CSU	Chronic Spontaneous Urticaria
CU	Chronic urticaria
CU-Q20L	Chronic Urticaria Quality of Life
DARPins	designed ankyrin repeat proteins
ESR	erythrocyte sedimentation rate
F1 + 2	Prothrombin fragment 1 + 2
FcεRI	high-affinity IgE receptor
FcεRIα	high-affinity IgE receptor alpha chain
HLA	Human Leukocyte Antigen
HUV	hypocomplementemic urticarial vasculitis
IFNγ	interferon gamma
IL-1	interleukin 1
IL-18	interleukin 18
IL-24	interleukin 24
IL-25	interleukin 25
IL-33	interleukin 33
IL-4	interleukin 4
IL-5	interleukin 5
IL-6	interleukin 6
Il-6sR	interleukin 6 soluble receptor
InH-AAE	idiopathic nonhistaminergic acquired angioedema
ITAMs	immunoreceptor tyrosine-based activation motifs
LCN2	serum Lipocalin-2
MC_T	tryptase-positive chymase-negative mast cells
MC_{TC}	tryptase-positive chymase-positive mast cells
MMP-9	matrix metalloproteinase-9
MPV	mean platelet volume
NGF	nerve growth factor
NSAID	non-steroidal anti-inflammatory drug
PG	Prostaglandins.
PGD2	prostaglandin D2
sgp130	soluble glycoprotein 130
Siglec	Sialic acid-binding immunoglobulin-like lectin
SYK	spleen tyrosine kinase
Th1	T helper 1
Th2	T helper 2
TPO	thyroid peroxidase
TSH	thyroid stimulating hormone
TSLP	thymic stromal lymphopoietin
UAS7	weekly urticaria activity score
USS	Urticaria Severity Score (USS)
UV	urticarial vasculitis

1 Definition

Urticaria is a common clinical condition characterized by the cutaneous appearance of wheals (hives), angioedema or both (Zuberbier et al. 2018).

Urticarial wheals are defined by three features: a central swelling of variable dimensions surrounded by an erythematous border; an intense sensation of itching or burning; a short-lived appearance with the skin returning to normal in less than 24 h (Zuberbier et al. 2018). Wheals are mainly due to vasodilation in superficial dermal causing swelling of tissues, local oedema and concurrent sensory neural activation which is associated to pruritus (Antia et al. 2018).

Angioedema is characterized by sudden swelling of the lower dermis and subcutis or mucous membranes (with occasional erythema), sporadic presence of pain and a slower resolution in comparison to wheals (up to 72 h) (Zuberbier et al. 2018). Angioedema is also caused by

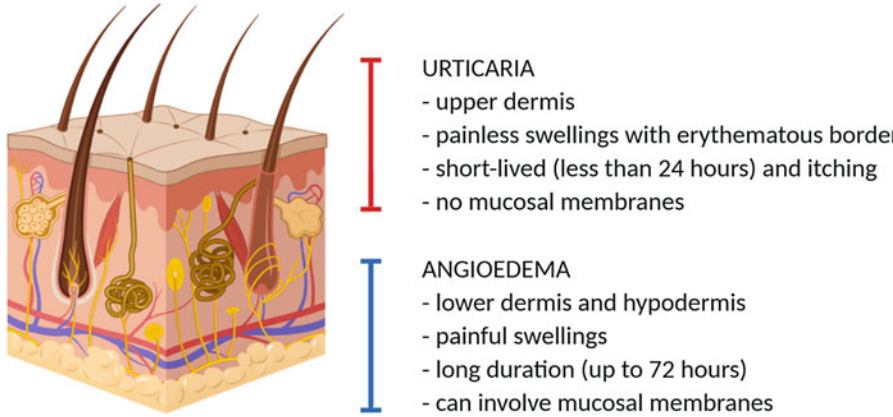

Fig. 1 Features of Urticaria and Angioedema Urticaria is characterized by painless erythematous and itching wheals which involve the upper dermis and are short lived. Angioedema presents as painful swellings with minimal or no skin alteration and long duration. It can involve also mucosal membranes

vasodilation, plasma extravasation and neural stimulation, but contrary to urticaria these phenomena occur in deeper layers of the skin (reticular dermis and subcutaneous tissue) (Antia et al. 2018) (Fig. 1).

2 Classification

Urticaria can have a wide spectrum of presentations and subtypes, which can typically coexist in the same patient. Acute urticaria (AU) is distinguished from chronic urticaria (CU) based upon its duration, with a defining period of less than 6 weeks (compared to a duration longer than 6 weeks for CU, Table 1A). In acute cases of urticaria, anaphylaxis should be excluded by evaluating for signs of respiratory, gastrointestinal, neurologic upset or hemodynamic instability (Antia et al. 2018). The presence of a clear external trigger (e.g. insect sting, food ingestion) or a suggestive past medical history should equally be red flags alarming the physician to consider urticaria as a possible feature of anaphylaxis (Estelle Simons Ledit 2013).

While most cases of acute urticaria remain idiopathic after history taking, the most common associated factors are respiratory infections (40% of cases), drug reactions (9,2%) and food reactions (0.9%) (Antia et al. 2018; Zuberbier et al. 1996).

Chronic urticaria can be divided into chronic inducible urticaria (CIndU) and chronic spontaneous urticaria (CSU). The subdivision is based upon the clinical reproducibility of wheals following exposure to a direct stimulus (e.g. cold, pressure, water, etc.) or absence of such trigger (Zuberbier et al. 2018). While CSU is considered as a single clinical entity, although multiple pathogenetic subsets may be present, CIndU is further split into several conditions based in the specific trigger mechanisms as presented in Table 1B. Behind the appearance of a minor disorder, chronic urticaria carries an important burden of disease for affected patients and their family members (Zuberbier et al. 2018). A reduction in objective well-being and subjective health has been observed in patients suffering from chronic spontaneous urticaria, especially when the condition is refractory to treatment or just partially responsive (Maurer et al. 2017a). Along with an impaired quality of life, chronic spontaneous urticaria is also associated with a considerable impairment in work productivity, which can be a result of the bothersome itching sensation and aesthetic disfigurement (in severe cases) (Maurer et al. 2017b; Maurer et al. 2016).

Rarely, urticaria can be the initial presentation of a systemic autoimmune, hematologic, autoinflammatory or neoplastic disorder (Zuberbier et al. 2018). Therefore, the presence

Table 1A The current classification distinguishes urticaria based upon its duration (acute when lasting less than 6 weeks, chronic when lasting for a longer time). Chronic urticaria is further subdivided into inducible and spontaneous forms. Patients with CSU have wheals that appear spontaneously, with no external trigger needed. On the contrary, patients with CIndU suffer from wheals only when exposed to specific physical triggers

Duration	Subtype	Description
Acute <6 weeks		
Chronic >6 weeks	*CSU*	Unknown trigger
	Inducible	Known trigger

Table 1B Classification of chronic inducible urticaria. Patients with CIndU suffer from wheals only when exposed to specific physical triggers. Sometimes, CIndU and CSU may coexist in the same patient

Subtype	Description	Test
Symptomatic dermographism	Urticarial lesions in response to pressure, rubbing or scratching (human contact or clothes) (Dice 2004). Wheals appear immediately after contact and remit within less than an hour	Fric test: Plastic tool used to evaluate the severity of dermographism reproducibly (Mlynek et al. 2013)
Acquired cold urticaria	Wheals after exposure to cold fluids, solids or gaseous substances	The reaction can be elicited by applying the cold provocation test (Zuberbier et al. 2018)
Heat urticaria	Hot objects induce the formation of wheals when brought in contact with the skin. Some familial cases have also been described (Radonjic-Hoesli et al. 2018)	A heat provocation test shall be performed for confirmation (Zuberbier et al. 2018)
Delayed pressure urticaria	Formation of skin lesions several hours after exposure to perpendicular pressure. It often coexists with CSU and other forms of physical urticaria (Radonjic-Hoesli et al. 2018)	Pressure test to verify and quantify angioedema (Zuberbier et al. 2018)
Solar urticaria	Exposure to sunlight, especially UV-A light. This condition is very rare (Radonjic-Hoesli et al. 2018)	The patient may be tested with light of different wavelengths (Zuberbier et al. 2018).
Cholinergic urticaria	It precipitates after an immediate increase in body temperature (e.g. hot baths, physical exercise, emotional stress, hot food) (Abajian et al. 2014)	Provocation testing (Zuberbier et al. 2018)
Vibratory angioedema	Angioedema occurs after local exposure of the skin to vibrations. Interestingly, a genetic mutation (ADGRE2) has been observed in the autosomal dominant variant of the disease (Boyden et al. 2016)	Testing with vibration (e.g. mixer) (Zuberbier et al. 2018)
Contact Urticaria	When the patient experiences contact with the eliciting substance, wheals appear which persist for a few hours. Contact urticaria may sometimes be an occupational disease (Williams et al. 2008)	Provocation testing with suspected substance (Zuberbier et al. 2018)
Aquagenic Urticaria	Rare form which occurs after contact with water, including body fluids such as sweat and tears	Diagnosis can be obtained by performing a water challenge test (Rothbaum and McGee 2016)

of atypical associated features should prompt the clinician towards a more extensive diagnostic approach.

3 Epidemiology and Genetics

Surveys about the lifetime prevalence of any form of urticaria yielded results ranging from less than 1% to more than 20%, depending on the age of patients, the methods of the study and its location (Antia et al. 2018; Weller et al. 2010). Both AU and CU have been more commonly observed in females, with an apparent ratio of 2 females for each male (Antia et al. 2018; Sánchez-Borges et al. 2015a; Amsler et al. 2014; Lapi et al. 2016; Kalogeromitros et al. 2011; Magen et al. 2013). Apparently, the gender gap in prevalence

seems to narrow among the elderly, the children and when considering some forms of CIndU (Cassano et al. 2016; Ban et al. 2014).

AU lifetime prevalence was reported in Europe with estimations going from 12% to 24%, qualifying therefore as a very common condition (Konstantinou et al. 2011; Pogorelov et al. 2016). As only a minority of patients with AU progress to the chronic form of disease, the prevalence of the latter condition is clearly lower. A study from the US estimated the 1-year prevalence of CU to be as low as 0.08%, while data from Europe reported a prevalence for the same period ranging between 0.38% and 0.8% (Lapi et al. 2016; Pogorelov et al. 2016; Zazzali et al. 2012).

In Spain, chronic urticaria was observed more commonly in patients between 25 and 55 years old (Gaig et al. 2004). In contrast, a recent Italian study observed a higher incidence of CSU among patients younger than 20 years and those older than 50 years old (Kalogeromitros et al. 2011). Other studies actually observed a lower incidence of all forms of urticaria in children, with the prevalence of any type of urticaria ranging between 3.4% and 5.4% (Antia et al. 2018; Dilek et al. 2016; Kjaer et al. 2008).

Urticaria is clearly a disorder with no Mendelian inheritance. Nevertheless, several HLA class II alleles were associated with CSU according to the results of a study conducted in 1999 on British patients (O'Donnell et al. 1999). A subsequent Italian study observed a higher prevalence of the disease among family members of patients, suggesting a familial inheritance. Later, additional HLA alleles (class I and class II) were also associated with the disease (Asero 2002; Coban et al. 2008).

4 Pathogenesis

Disclosing the pathophysiology of urticaria appears to be the principal need to bring successful treatment in a clinical setting. Nowadays, it is widely accepted the thesis involving mast cells as the principal mediators of damage. The wheal is microscopically characterized by a pro-inflammatory microenvironment generated by the degranulation of activated mast cells which determine the release of a great amount of soluble molecules such as histamine, leukotrienes, prostaglandins (PGs) and others cytokines.

This pathological niche presents high amount of mediators that have the ability to shape the infiltrate enhancing the activity of the homed cells leading to the perpetration of the damage. The analysis of soluble proteins from lesional skin suggests a mixed Th1/Th2 response by the presence of high amount of interleukin IL-4, IL-5, IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) as well as interferon-gamma (IFNγ) (Caproni et al. 2005; ELIAS et al. 1986; Kay et al. 2015).

These inflammatory factors determine the presence of a perivascular aggregation of immune cells mainly composed by mast cells, lymphocytes, monocytes, neutrophils, eosinophils (Vonakis and Saini 2008) and basophils (Ying et al. 2002); moreover, markers of vascular leakage and angiogenesis were found to be highly expressed on the surface of endothelium of the affected vessels (Kay et al. 2014).

4.1 Acute Urticaria

Considering the acute form of urticaria, the pathophysiology has been less extensively studied with respect to the abnormalities occurring in the chronic condition. Despite its higher frequency in population, AU presents a short duration of disease as well as effective treatments. Precipitating factors have been described in less than 50% of cases. The most common one is the presence of a concomitant viral infection, followed by drugs, food and insect sting reactions (Zuberbier et al. 1996; Kulthanan et al. 2008). Along with viruses, several reports described association with bacterial infections such as cystitis and tonsillitis (Wedi et al. 2009), instead, consumption of raw fish and exposure to Anisakis simplex nematodes, was highlighted only in some studies (Wedi et al. 2009; Del Pozo et al. 1997).

Scientific evidence identifies the same pathological alterations in both forms. An abnormal

release of histamine, platelet-activating factor and cytokines by activated mast cells leads to vasodilation, increased vascular permeability and stimulation of sensory nerve endings in the affected skin.[1] Furthermore, mediators released from mast cells may act as chemo-attractants for cells of the immune system, such as eosinophils, neutrophils and lymphocytes. As a consequence, the affected dermis becomes inflamed (Radonjic-Hoesli et al. 2018).

4.2 Chronic Urticaria

The chronic form, defined as a spontaneous or induced occurrence of wheals, is considered to be caused by a persistent derangement in functioning of mast cells. The inappropriate and uncontrolled degranulation of those determines the clinical manifestation with the appearance of the short-lived typical lesions.

Even if the pathogenesis of CIndU is clearly dependent upon definite extrinsic factors which activate and enhance mast cells degranulation (Tables 1A and 1B), the pathogenesis of the spontaneous form remains elusive. Because of the peculiar features and not well understood role of mast cells in the human organism, several elements have been analysed tempting to define cellular and molecular pathways responsible of CSU. Recently, the alteration in mast cells activation has been mostly attributed to complex mechanisms of autoimmunity involving various component of the immune system besides to complement cascade and coagulation.

4.2.1 Cellular Alterations

Within skin lesions, a mixed perivascular pro-inflammatory infiltrate can be observed. Attracted by chemokines which are mainly released by mast cells, eosinophils, monocytes, basophils and T helper cells penetrate the skin layers occupying the perivascular space. Interestingly, a peculiar mixed Th1 and Th2 responses seems to be present, with a concurrent increase of both spectra main mediators (Radonjic-Hoesli et al. 2018; Kay et al. 2015; Ying et al. 2002).

Strong evidence in support of the autoimmune pathogenesis of CSU is certainly the documented presence of autoreactive CD4+ T cells targeting FcεRIα in subjects with the disease. In a recent study, these lymphocytes were detected in more than a quarter of investigated patients, while they were completely absent in controls. They were associated with a Th1 phenotype, with secretion of IFN-γ (Auyeung et al. 2016).

Mast Cells

Mast cells are derived from bone marrow CD34+, CD117+ (Kit), CD13+ pluripotent progenitor cells that mature under the local environment of the tissues into which they migrate (Kirshenbaum and Metcalfe 2006; Bandara et al. 2015). Studies focusing on the content of their granules led to identify two different subtypes which present different interaction with the other cells of immune system as well as a dissimilar localization in the human body. In particular, mast cells which are tryptase-positive but chymase-negative (MC_T) (Irani and Schwartz 1989) which contain complete scroll, are located at mucosal tissues, such as the intestine, lung and nose, are T-lymphocyte dependent and are increased in number in allergic disease (Irani and Schwartz 1989; Otsuka et al. 1995). The other subtype is defined to be constituted by both tryptase and chymase-positive granules (MC_{TC}) which appear to form grating or lattice structure (Irani and Schwartz 1989). They are found primarily in the skin and gastrointestinal submucosa and are independent of lymphocytes (Smith et al. 1995).

The role of mast cells in CSU is consensually acknowledged. However, it's still controversial whether they are increased in numbers in patients with the disease. While some studies supported this hypothesis, others found no association (Saini and Kaplan 2018). Only a few studies that analysed the presence of mast cells in the lesional skin distinguished between MC_T and MC_{TC}. One of these, in particular, highlighted how there is no difference between the number of MC_{TC} between CSU patients and heathy ones; however, the presence of the subtype MC_T varies significantly (Bradding et al. 1995).

Evidence for mast cell degranulation come firstly from the measurement of total serum tryptase levels, which appear to be slightly elevated in subjects with CSU compared to both healthy and atopic subjects even if still within the normal range (Ferrer et al. 2010). According to some evidence, a functional defect in these cells activation may lead to increased histamine release in CSU (Bédard et al. 1986; Jacques et al. 1992). This alternative hypothesis attributes the chronic evolution of acute urticaria to a defect in mast cells intracellular signalling, rather than autoimmune disturbances (Bracken et al. 2019). Findings in support of this assumption rely on release tests which demonstrate, by the use of 48/80-induced histamine responses via skin chambers, how mast cells coming from CSU patients appear to be more prone to degranulate (Bédard et al. 1986; Jacques et al. 1992).

The molecular basis of the altered response appears to lies in the structure of FcεR1, which contains immunoreceptor tyrosine-based activation motifs (ITAMs). After phosphorylation, ITAMs allow the activation of spleen tyrosine kinase (SYK) and downstream pathways which eventually elicit the degranulation of mast cells (Bracken et al. 2019). Mast cells from CSU patients, when cultured in vitro, were observed to release significantly higher levels of histamine than their counterparts from healthy controls.

Activated mast cells were shown to express significantly higher levels of SYK during the same experiment (Saini et al. 2009). Interestingly, a subsequent study did not found SYK to be upregulated from anti-FcεRI autoantibodies. This implies that the upregulation of SYK observed in a subset of CSU patients depends upon causes other than autoimmunity or, more accurately, other than autoantibodies (MacGlashan 2019).

The presence of activated mast cells has profound effects on local microenvironment. Some recent evidence points the attention on the ability of these cells to produce high amount of neuropeptides, in particular NGF (Aloe et al. 1994; Peters et al. 2011), which is markedly elevated in subject affected by allergic diseases and CSU (Bonini et al. 1996). NGF is a member of neurotrophin, has pivotal roles for the development and survival of nociceptive neurons but also is involved in chronic inflammation maintaining and promoting the proliferation and activity of lymphocytes, neutrophils, eosinophils and mast cells (Minnone et al. 2017).

In CSU has been demonstrated how NGF is able to act stimulate the proliferation of mast cells besides act as a chemotactic factor. This evidence could be at the base for a pathological loop in which the activated mast cells through the stimulation of sensory nerves could enhance the immune infiltrate supported by inflamed nerves (Fig. 2) (Minnone et al. 2017).

Basophils

Basophils are circulating granulocytes which can express IgE receptors, release histamine and produce several cytokines, such as IL-4, IL-13 and others, in response to IgE receptor activation (Saini and Kaplan 2018; Schroeder 2009; Raap et al. 2017). Blood basophils in patients with CSU were characterized by multiple abnormalities. Along with a reduction in their number (basopenia), reduced histamine release in response to anti-IgE (basophils hyporesponsiveness) and basophil infiltration of skin lesions have been observed (Vonakis and Saini 2008; Saini and Kaplan 2018; Rorsman 1962). Several alterations in the function and number of basophils have been observed in CSU patients suggesting a recruiting from the bloodstream into urticarial skin lesions (Grattan et al. 2003).

Based on the response to IgE-receptor-mediated histamine degranulation, it is possible to identify two different subsets of basophils in CSU patients which are confirmed by a study monitoring CD63 induction after IgE-receptor activation (Rauber et al. 2017). Improvements in both basopenia and basophil IgE-receptor abnormalities are seen in natural remission of CSU and point to basophils as contributor to disease (Eckman et al. 2008). Even if the pathways involved in the processes which recruit basophils to skin lesions are not yet elucidated, some evidence focused the attention on the prostaglandin D2 (PGD2) pathway and the chemoattractant receptor homologous molecule

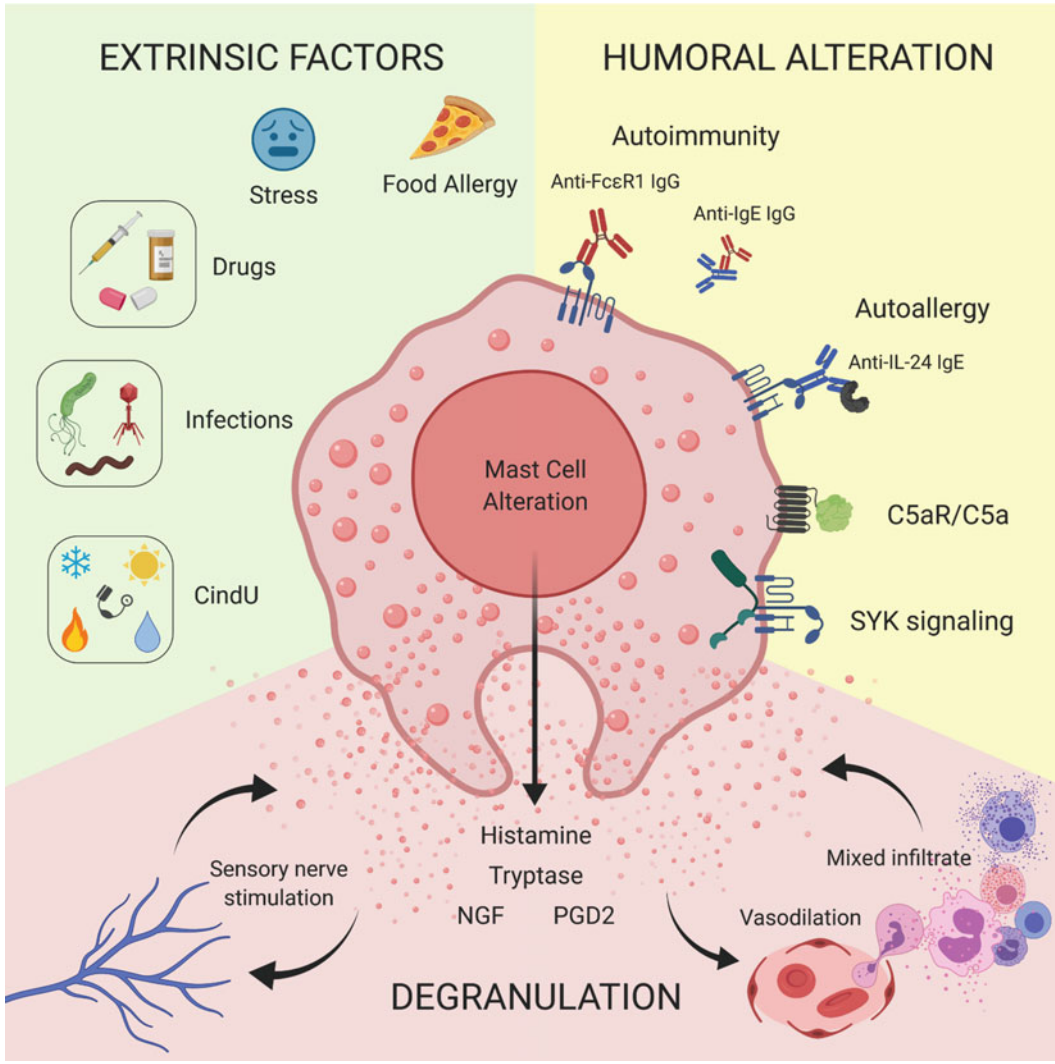

Fig. 2 Possible mechanisms of mast cell activation in urticaria

Extrinsic factors (green section). Several extrinsic elements can exacerbate urticaria via mast cells activation. Infections and drugs are identified as one of the most frequent precipitating factors. Some evidence demonstrate how emotional stress has been strictly linked to a worsening of skin symptoms instead, foods and food additives have been implicated mainly as a consequence of food allergy. CindU are well-known examples of triggered urticaria

Humoral alteration (yellows section). The main pathogenic mechanisms actually identified and under validation are: Autoimmunity**.** IgG autoantibodies (IgG) target IgE-receptors (FcεR1) on mast cells (MC). This leads to dimerization of receptors and mast cell activation, with consequent degranulation (DMC). Concurrently, formation of complement fragments (C5a) and binding to C5a receptor (C5aR) on mast cells enhances the process. Autoallergy**.** IgE antibodies (IgE) targeting human proteins such as interleukin 24 (IL-24) are present in serum. These bind to FcεR1 via their Fc region, leading to allergic reactions against "autoallergens". Intracellular signalling defects**.** An abnormal activation of spleen tyrosine kinase (SYK) in mast cells of patients with chronic urticaria leads to increased intracellular signalling and consequent degranulation without external triggers

Degranulation (red section). Mast cells degranulation could be facilitated by intrinsic cell defects which diminishing the activation threshold lead to an enhanced exocytosis. The release of histamine, tryptase, PGD2 and NGF determine an increase in vascular permeability causing the extravasation of several inflammatory cells. Perivascular mixed infiltrate interacts with tissue mast cells generating a pathological loop which worsen and maintain a pro-urticaria microenvironment. The same auto stimulatory condition could be occurring with free nerve endings by secretion of NGF

expressed on the Th2 cell (CRTH2) (Oliver et al. 2016).

Moreover, data from omalizumab phase III trials in CSU shows a correlation between the clinical response and that improvement in basopenia (Saini et al. 2017).

Recent finding observed increased IL-31 in skin as well as serum levels of CSU patient (Raap et al. 2010). This molecule is considered to be the major player inducing pruritus in skin diseases such as atopic dermatitis but also determine a powerful chemotactic action on basophils recruitment. This indicates that IL-31 plays a role in the orchestration and accumulation of basophils in inflammatory skin diseases; furthermore, it has been widely demonstrated how basophils are the main cellular sources of IL-31 in skin lesions of CSU patients (Raap et al. 2017). The inhibition of this pathological loop could be thus of therapeutic interest in controlling itch-related symptoms as well as inducing the remission of disease (Fig. 2).

4.2.2 Humoral Alterations

The initial study which provided strength to this hypothesis was the development and testing of the autologous serum skin test (ASST) (Grattan et al. 1986). More than three decades ago, few patients with chronic spontaneous urticaria were drawn blood; serum was separated from it and reinjected intradermally with the result to develop wheals when exposed (Grattan et al. 1986). Clearly, this seemed to imply the presence of an intrinsic serum factor triggering urticaria; however, this finding was later doubted when evidence came out that a substantial percentage of healthy controls also developed positive ASST reactions (Taskapan et al. 2008).

Thyroid autoimmunity, especially Hashimoto's thyroiditis, has also been associated with CSU for a long time (Levy et al. 2003; Nuzzo et al. 2011). This seemed to provide evidence of a common autoimmune mechanism or predisposition. According to recent evidence, which emerged from a European multicentric study (the PURIST study) (Schoepke et al. 2019), a subset of patients with purely autoimmune pathogenesis may exist, although its relative weight appears minor. Defined three criteria as a red-flag of derangements in immune function, only 8% of the patients studied fulfilled all the conditions, even if this group had higher activity of the disease (UAS 7), lower IgE levels and higher anti-TPO IgG levels.

Besides the association with thyroid autoimmunity, a high frequency of antinuclear antibodies (ANA) has also been observed among these patients (Viswanathan et al. 2012). However, their meaning in CSU is poorly understood and, as ANA are well known to occur in a considerable fraction of the healthy population, they bear no practical use in CSU (Viswanathan et al. 2012).

On the contrary, antibodies specific to CSU and relevant to its pathogenesis are those targeting FcεR1. These were described for the first time in a group of 26 patients with CSU. It was hypothesized that they could act similarly to anti TSHr-antibodies in Graves disease, leading to the activation, rather than the neutralization, of their target (Hide et al. 1993). Specifically, these IgG antibodies bind to FcεRI on mast cells, leading to their activation and degranulation. This mechanism alone, due to activating autoantibodies, seemed to explain up to one quarter of cases of CSU (as anti- FcεR1 IgGs are prevalent in about 25% of patients) (Niimi et al. 1996).

Fascinatingly, in a small subset of patients, anti-IgE autoantibodies were also observed (Niimi et al. 1996). This may sound puzzling to those who are well acquainted with the therapeutic effectiveness of anti-IgE monoclonal antibodies (eg. Omalizumab) in CSU. However, a recent study conducted on asthma patients demonstrated that naturally occurring anti-IgE IgGs are quite frequent and not necessarily inhibitory (Chan et al. 2014). Some of these actually lead to activation of basophils, a finding which may also be coherent with their presence in CSU patients.

Along with humoral autoimmunity, a role for humoral "autoallergy" has been postulated in CSU. Autoallergy refers to the presence of IgE antibodies against human proteins, which would be capable of inducing mast cells degranulation without extrinsic triggers. The first autoallergen to be identified in CSU was thyroid peroxidase (TPO). Anti-TPO IgEs were shown to be

significantly more prevalent in patients than in controls (Altrichter et al. 2011). Subsequently, interleukin 24 (IL-24) was identified as a more sensitive and specific autoallergen for CSU (Schmetzer et al. 2018). Anti-IL-24 IgEs were additionally shown to be able to bind mast cells and lead to histamine release, which is a needed condition to prove their pathogenicity (Schmetzer et al. 2018).

Despite that, some difficulties arise when trying to develop a coherent model of pathogenesis for autoallergens and their antibodies. In fact, TPO is not present in the skin and IL-24, which is present in the epidermis, is not known to be found in the dermis as well (Poindexter et al. 2009). As the epidermis is normal in CSU, a definite role of autoallergy can't be ultimately proven (Fig. 2) (Kaplan 2019).

Complement

Whereas autoantibodies constitute the humoral arm of the adaptive immune system, the complement system provides innate immunity with an equally effective means of molecular defence. Unfortunately, when complement derails from its normal function, it may compound damage in a dysregulated immune system.

Soon after the discovery of autoantibodies targeting IgE receptors, it was found that a subset of these was able to activate mast cells only *in vivo*. This was hypothesized to be due to the exclusive *in vivo* presence of complement and its fragments, which could bind to antibodies and complement receptors (C5aR.) on mast cells (Fiebiger et al. 1995).

Purified C5a fragments were later tested for their effects upon histamine release in the presence of anti-IgE receptor IgGs. C5a was associated with a significant increase in histamine release from mast cells, when compared to complement-depleted serum (Ferrer et al. 1999). It was therefore suggested that IgGs cross binding FcεRI on mast cells could have a stronger degranulating effect in the presence of higher amounts of activated complement fragments (Fig. 2) (Kikuchi and Kaplan 2002).

Coagulation

Although the coagulation cascade is not directly linked with the immune system, its relevance in the pathogenesis of CSU has been supported by several studies (Asero et al. 2007). After initial findings of an increased activation of the coagulation, use of anticoagulant drugs was considered as a valid adjuvant in the treatment for CSU (although no increase in the risk of thrombosis was observed in these patients) (Cugno et al. 2010).

The increased activation of fibrin and other coagulation factors may be the result of vascular damage taking place in the affected skin. The same group of researchers also showed a prompt decrease in levels of D-Dimer (a degradation product of fibrin) in patients with a clinical response after being treated with either cyclosporine or omalizumab (Asero 2015; Asero et al. 2017).

4.2.3 Extrinsic Precipitating Factors

As it is the case for AU, the chronic spontaneous form has also been associated with several extrinsic factors. Among these, infections of viral, parasitic, bacterial or fungal aetiology have all been implicated in causing chronic spontaneous urticaria or its exacerbations (Antia et al. 2018). Helicobacter pylori was long believed to play a causative role in a significant subset of patients.

A study highlighted how the eradication of the bacterium had provided significantly beneficial effects to patients with chronic spontaneous urticaria, with a complete or partial remission of symptoms (Di Campli et al. 1998). Unfortunately, results were not replicated by subsequent studies, which didn't found any association with H. pylori, nor any improvement of CSU eradication therapy (Curth et al. 2015; Kohli et al. 2018).

Several foods and food additives have been implicated and extensively studied in the pathogenesis of chronic spontaneous urticaria (Antia et al. 2018). Patients may sometimes indicate certain foods as the cause of their symptoms and consequently develop avoidance mechanisms when choosing what to eat. However, studies

which investigated the presence of urticarial symptoms after oral food challenge only observed them in a small minority of patients with such claims (Hsu and Li 2012; Chung et al. 2016).

Drugs can exacerbate urticaria through different mechanisms. ACE inhibitors are well known to cause angioedema by causing an increase in the amounts of bradykinin (Scalese and Reinaker 2016). Nonsteroidal anti-inflammatory drugs (NSAIDs) may also induce urticaria, either through an allergic (IgE-mediated) reaction or through the inhibition of COX-1 and increased production of leukotrienes (Antia et al. 2018).

Emotional stress has also been associated with chronic spontaneous urticaria. Patients suffering from the disorder suffer from higher rates of depression, anxiety and somatoform disorders with respect to the general population. However, it's unclear whether this is a consequence of coping with the disorder or a possible predisposing factor (Fig. 2) (Uguz et al. 2008).

5 Diagnosis

According to the latest guidelines AU is to be considered as a self-limiting disorder, which requires no investigation unless a couple of specific features are present. Namely, these are the presence of a type I food allergy (IgE-mediated) or of another eliciting factor such as NSAIDs (or other drugs) (Zuberbier et al. 2018). In these cases, the patient should be counselled towards allergy tests and avoidance of re-exposure to proven precipitating factors.

In CU, the workup is more extensive. The most relevant component of the investigation is the history taking, which, if conducted properly, usually spares the physician and the patients time-consuming, costly and often improper laboratory testing.

5.1 Diagnostic Workup

A summary of the crucial questions in history taking and their diagnostic role has been included in Table 2, still based upon the latest international recommendations (Zuberbier et al. 2018).

After conducting history taking, physical examination should be performed. Along with a general survey of the patient, attention should be focused on features of the skin lesions (when present at the time of the visit). Eventually, each form of CIndU should be confirmed with the appropriate testing (see Tables 1A and 1B).

CSU wheals may have variable appearance, but they should always blanch with pressure and leave no trace after 24 h. In patients with typical features of CSU, lab testing should be restricted to a differential blood count, ESR and CRP. In patients with atypical features (e.g. wheals not resolving within 24 h, presence of angioedema only) or other associated symptoms, a more extensive workup may be appropriate. Testing for Helicobacter pylori, functional autoantibodies presence (e.g. ASST), thyroid autoimmunity, allergy tests, vasculitis (e.g. skin biopsy) or other systemic disorders may be warranted depending upon the history (Zuberbier et al. 2018).

5.2 Biomarkers of Diagnosis and Severity

Biomarkers are clinical features (clinical biomarkers) or molecules present in serum (molecular biomarkers) which are able to offer some diagnostic, therapeutic or prognostic information. They clearly depend upon the disease pathogenesis and are one of the most important fields of clinical research in many conditions, including CSU. Clinical biomarkers for diagnosis, stratification of disease and treatment response have been observed in CSU. These include age and gender (Folci et al. 2018). Being female has been associated with a more prolonged clinical course and a worse quality of life, while an association of older age and longer duration of disease has also been established (Gregoriou et al. 2009; Hiragun et al. 2013).

The presence of angioedema is particularly taken in consideration because of a strict correlation to a less favorable prognosis (Toubi et al.

Table 2 History taking in chronic urticaria. A list of items which should be assessed when first visiting a patient with urticaria and/or angioedema

Anamnestic item	Diagnostic relevance
Time of onset	Crucial to classify urticaria as acute or chronic (>6 weeks)
Shape, size, frequency, and duration of wheals	Although wheals may have variable appearance and size, they last characteristically less than 24 h in CSU. When lasting longer than 24 h, the suspicion of an urticarial vasculitis should arise
Presence of angioedema	When angioedema is the main complaint the clinician should suspect acquired angioedema (testing of C4, C1-inhibitor levels and function) and hereditary angioedema (gene mutation analysis)
Associated symptoms (such as arthralgias, bone pain, fever, abdominal pains)	This item is fundamental to decide when to extend the laboratory testing in the suspicion of a systemic disorder, with urticaria as its presenting feature
Family and personal history of wheals and angioedema	A positive family history for angioedema is quite suggestive of hereditary angioedema (Tosi 1998; Pappalardo et al. 2000)
Induction by external physical agents or physical exercise	The patient should be asked whether he can "make his wheals come". In this case, a form of CIndU is likely present and the specific trigger should be investigated. In some patients, CSU and CIndU coexist, so that they are not exclusive categories
Association with certain foods or drugs (e.g. NSAIDs, ACEi.)	This is fundamental to rule out the presence of a pharmacological trigger
Allergies, autoimmune disorders, gastrointestinal or other disease	This item allows a better understanding of the overall patient's health status and may be helpful in the setting of suspected differential diagnosis
Previous treatment and responsiveness	It's fundamental to ask about previous treatment in order to implement correctly the stepwise approach which is adopted in CSU
Previous diagnostic testing	This is often useful to avoid repeating laboratory testing

2004; Champion et al. 1969). Exacerbations occurring with the use of aspirin or non-steroidal anti-inflammatory drugs (NSAID) have been widely described as being related to a more severe and chronic disease (Sánchez-Borges et al. 2015b; Shin et al. 2015).

For what concerns molecular biomarkers, a considerable number is present, even if no one of them has yet gained the clinical practice. C reactive protein (CRP) is certainly one of the most important and reproducible. High CRP levels were demonstrated to be associated with higher activity of disease and quality of life impairment (Kolkhir et al. 2017; Kolkhir et al. 2018). Another molecule with marked inflammatory activity, interleukin 6 (IL-6), was also found to be increased (Kasperska-Zajac et al. 2015). Furthermore, Vitamin D, well-known because of its crucial role in bone metabolism, less because of its immunomodulatory activity, has been implicated in the pathogenesis of chronic urticaria. Apparently, depletion in Vitamin D is associated with an increased disease severity. As a consequence, it may be an effective marker with potential therapeutic implications (Vitamin D supplementation) (Piemonti et al. 2000; Holick and Vitamin 2007; Woo et al. 2015).

As it was previously described, D-Dimer levels were long thought to be an effective marker of response to treatment, especially when high before administration (Takeda et al. 2011). However, recent evidence contradicts this view and actually confirms the validity of D-dimer only as a marker of CSU severity.

In order to evaluate patients who are less likely to respond to Omalizumab promptly, due to the presence of anti-IgE receptor IgGs, the basophil histamine release assay (BHRA) may be used. BHRA evaluates the presence of IgGs targeting FcεRI in serum. In patients who test positive, omalizumab will take time to be effective. This is due to the need for all FcεRI on mast cells to be uncovered from IgE (which occurs immediately) and slowly decay (over several weeks) (Grattan et al. 1986; Folci et al. 2018; Metz et al. 2017; Saini and MacGlashan 2012).

Table 3 Biomarkers of diagnosis, prognosis and severity

Biomarker		Diagnosis	Prognosis and severity	
			Better	*Worse*
Clinical	Age	–	Young pts	Older pts
	Gender	–	Male	Female
	Duration of CSU	–	Less than 1 yr	Longer than 1 yr
	Angioedema	–	Absent	Present
	NSAID exacerbation	–	Not associated	Associated
Molecular	Anti-IL-24 IgE	Positive association	–	–
	IL-6	–	–	High levels
	IL-6 sR	–	–	High levels
	Sgp130	–	–	High levels
	IL-18	–	–	High levels
	MMP-9	–	–	High levels
	CRP	–	–	High levels
	D-dimer	–	–	High levels
	F1 + 2	–	–	High levels
	Vitamin D	–	–	Low levels
	MPV	–	–	High values
	Basophils count	–	Normal number	Low number
	CD203c-basophils	–	–	Increased

MMP-9 Metalloproteinase-9, *CRP* C reactive protein, *F1 + 2* Prothrombin fragment 1 + 2, *Il-6sR* Interleukin 6 soluble receptor, *sgp130* Soluble glycoprotein 130, *mpv* mean platelet volume, *ESR* Erythrocyte sedimentation rate, *CRP* c-reactive protein

Other biomarkers, such as interleukin 18 (IL-18) and matrix metalloproteinase-9 (MMP-9), have also been considered. IL-18 may be involved in the recruitment of eosinophils in skin affected from urticaria, while MMP-9 may be involved in the migration of immune cells by remodelling tissue extracellular matrix (Novick et al. 2001; Wang et al. 2001; Ram et al. 2006; Song et al. 2013; Belleguic et al. 2002). However, results are far from being conclusive and they will need validation from other groups.

Eventually, IL-24 should be mentioned once again. If a standardized assay (e.g. ELISA testing) for the quantification of anti-IL-24 IgE were developed, it would appear more feasible to start considering autoallergy in the clinical setting. Also in this case, although results are still preliminary, they seem to be quite promising (Table 3).

5.3 Differential Diagnosis

A broad spectrum of disorders is included in the differential diagnosis of chronic urticaria, with several of these conditions being rare but severe systemic disorders (Radonjic-Hoesli et al. 2018). The clinician should be particularly careful when urticaria is associated with other signs and symptoms or presents with atypical features (Radonjic-Hoesli et al. 2018). When wheals last for longer than 24 h, lesions are burning more than itching and don't disappear after digital pressure or the patient suffers from a systemic autoimmune disorder (such as systemic lupus erythematosus or primary Sjogren's syndrome), urticarial vasculitis (UV) may be present. Several other autoimmune, autoinflammatory and hematologic disorders may likewise present with urticaria (a summary of the most relevant conditions with their distinctive features has been included in Table 4).

6 Treatment

While treatment of acute urticaria has remained roughly the same in the last decades, the approach to management of chronic urticaria has been

Table 4 Main differential diagnoses of chronic urticaria

Diagnosis	Peculiar features
Urticarial vasculitis (UV)	The patient may present with wheals lasting longer than 1 day and cutaneous purpura. UV is a small-vessel vasculitis characterized by inflammatory injury of the capillaries of the dermis and the postcapillary venules (Jachiet et al. 2015). In order to reach the diagnosis, a skin biopsy is needed. UV can be further split into a normocomplementemic and a hypocomplementic (HUV, defined by low C1q levels, normal C1-inhibitor, frequent presence of anti-C1q antibodies) subtype. While normocomplementemic UV is usually idiopathic, HUV is usually associated with SLE or SS (Jachiet et al. 2015)
Bullous pemphigoid	In this systemic autoimmune disease, autoantibodies target hemidesmosomes and cause subepidermal blistering and skin detachment (Feliciani et al. 2015). However, the characteristic bullae do not appear in a minority of patients (20%), so that an urticarial rash and intense itching may be the only presentation (Bech et al. 2018)
Cryopyrin-associated periodic syndromes (CAPS)	Urticaria is almost invariably present in CAPS (consisting of familial Cold autoinflammatory Syndrome, Muckle-Wells Syndrome or neonatal Onset Multisystem Inflammatory Disease) together with recurrent fever bouts, arthralgias, eye inflammation and other symptoms which may be exacerbated by exposure to cold (Kuemmerle-Deschner et al. 2017). The disorder is mediated by an increased secretion of interleukin 1 (IL-1), due to a genetic mutation, and can be treated effectively with IL-1 blockade (e.g. anakinra, canakinumab)
Adult-onset Still's disease (AOSD)	AOSD is defined by recurrent bouts of fever, a typical salmon-coloured evanescent rash, a neutrophilic leukocytosis and arthralgias. Additionally, lymphadenopathy or splenomegaly, along with liver dysfunction, may be present (Yamaguchi et al. 1992). Urticaria has been described as a presenting feature of AOSD (Yamamoto 2012)
Schnitzler's syndrome	It's defined by the presence of fever, arthralgia, lymphadenopathies and urticaria in the presence of a monoclonal gammopathy (Lipsker et al. 2001). The disease has been grouped within autoinflammatory syndromes due to the pathogenic role of IL-1 and other cytokines (the chemoattractant CCL2). Besides, in some cases, it has been successfully managed with IL-1 blockade (de Koning et al. 2007; Krause et al. 2019)
Urticaria pigmentosa	This is a form of cutaneous mastocytosis which appears as a maculopapular rash of tan to brown colour which usually spares the palms and soles. Required investigations include serum tryptase and skin biopsy, which shows the presence of mast cell aggregates and increased number of mast cells in cutaneous mastocytosis (Macri and Cook 2019)
Breast, prostate and colon cancer	Some case reports have been published in which CSU was a paraneoplastic phenomenon in the setting of solid cancer (breast, prostate and colorectal cancer) (O'Donnell and Havyer 2014; Kasi et al. 2016; Baroni et al. 2012; Santiago-Vázquez et al. 2019)

revolutionized by the development of biologic drugs. Omalizumab is now the recommended drug in patients with CSU refractory to antihistamines treatment. Soon enough, a new generation of biologic and target drugs promises to further reduce the fraction of patients who does not respond fully to available therapies.

6.1 Acute Urticaria

Emergency physicians and general practitioners are often involved in the management of acute urticaria. Being described as a self-limiting condition, its treatment was not discussed by the most recent guidelines on urticaria (nor the previous ones), where it was just suggested that possible provoking factors should be avoided and symptomatic relief should be warranted (Zuberbier et al. 2018; Zuberbier et al. 2014). Previous literature on this topic is equally sparse. A short course of prednisone was proven to be effective in obtaining a quicker response in one trial, while in a nationwide survey conducted in the US, physicians reported the use of histamine (H1) antagonists and prednisone in affected children (Pollack and Romano 1995; Beno et al. 2007). In a recent review written by a worldwide expert on allergy and urticaria, it's suggested that H1 antihistamines are given up to four times a day, with an additional short course of steroids when severity requires it (eg. 40 mg of prednisone for 3 days, tapered by 5 mg/day or stopped without tapering) (Kaplan 2019). Second generation

H1 antihistamines (eg. cetirizine, levocetirizine, loratadine) are recommended over first generation ones due to improved safety profile, especially a lower incidence of drowsiness (which can still be present, especially when more than one tablet is taken daily) (Snidvongs et al. 2017).

6.2 Chronic Urticaria

The treatment of chronic urticaria depends on the presence of specific trigger factors, as it occurs in CIndU, or the absence of such, as in CSU. Importantly, the physician should acknowledge the difficulties experienced by the patient coping with a long-lasting disorder with no curative treatment. In order to provide the most effective solution without exposing patients to unnecessary risks, a stepwise approach should be followed. Corticosteroids should generally be withdrawn from therapy due to their profile of severe side effects in chronic use.

6.2.1 Chronic Inducible Urticaria

The management of CIndU clearly involves the avoidance of physical stimuli, although this is rarely possible. While it may be feasible to substitute latex products with other equivalent ones in the case of a contact urticaria, it may be more complex to avoid sunlight, exposure to cold or to water. In the case of delayed pressure urticaria, it's important to make the patient aware that by using wider handles for heavy bags the surface in contact with the skin is increased and, as a consequence, the pressure exerted is reduced (Zuberbier et al. 2018). Second generation H1 antihistamines have been successfully used in acquired cold urticaria, where four daily dosage (i.e. 20 mg desloratadine daily) was associated with improved clinical course with respect to lower dosages and placebo (Siebenhaar et al. 2009).

In those forms of inducible urticaria which are responsive to antihistamines, these are clearly the indicated therapy as long as needed. However, delayed pressure urticaria is unresponsive to these (Kaplan 2019). For these and other patients refractory to antihistamines, omalizumab has proven effective and safe in several studies (Metz et al. 2014; Quintero et al. 2017; Maurer et al. 2018). For the few patients who don't respond to omalizumab, no effective pharmacological treatment is available. Patients would clearly respond to steroids but the side effects of a prolonged treatment would almost certainly offset the benefits (Kaplan 2019).

6.2.2 Chronic Spontaneous Urticaria

Management of CSU is a careful process characterized by an add-on strategy to achieve the best control of disease, if not a complete remission.

Identification and Avoidance of Aggravating Factors

When reported in the course of history taking, drugs suspected of exacerbating CSU should be withdrawn from therapy and substituted with others, if possible. Other factors which have been associated with CSU are infections, such as H. pylori colonization. As previously described, the association between H. pylori and CSU has not been proven conclusively. However, when colonization is found, eradication therapy should be pursued, also because of the association of H. pylori with several other disorders (e.g. gastric cancer) (Zuberbier et al. 2018; Curth et al. 2015; Kohli et al. 2018). Reduction in emotional stress and avoidance of certain foods may also provide some degree of benefit, although this is questionable and not strongly supported by available research.

Pharmacological Management: A Stepwise Approach

The pharmacological management of CSU begins, as with all types of urticaria, with second generation, H1 antihistaminergic drugs. These are preferred over first generation H1 antihistamines because of their lower propensity to cause drowsiness. According to the most recent guidelines on treatment, these drugs are roughly equivalent, and patients may choose any of them (e.g. cetirizine, levocetirizine, desloratadine, ebastine, fexofenadine). However, the use of multiple antihistamines at the same time is not

recommended (Zuberbier et al. 2018). In many patients, standard dosage is not effective and it may need to be escalated up to four times in order to warrant remission. Although this approach is also supported by urticaria guidelines, it may pose the patient at a higher risk of sleepiness and is not necessarily compliant to all countries prescribing regulation.

When high doses of regularly administered antihistamines are not effective, omalizumab should be prescribed as an add-on to therapy. Omalizumab is a humanized monoclonal IgG immunoglobulin which targets IgE and prevents their binding to FcεRI (Tonacci et al. 2017). With time, uncovered FcεRI on basophils and mast cells undergo a process of slow decay and reduction in number (Saini and MacGlashan 2012). Omalizumab was administered for the first time in patients with CSU in a small study carried out in 2008 (Kaplan et al. 2008). The effectiveness and safety of the drug was later confirmed by one phase two and three phase three trials (Saini et al. 2011; Maurer et al. 2013; Kaplan et al. 2013; Saini et al. 2015).

These trials brought evidence that doses of 150 mg and 300 mg of omalizumab monthly were both effective, although the 300 mg dose was clearly more effective than the lower one. About 40% of patients reached complete remission and more than half (around 60%) obtained partial remission (calculated with UAS7 score lower than 6) (Kaplan 2019). It also emerged how patients often relapsed when the drug was discontinued, which didn't seem to affect the course of the disease in the long term. Interestingly, omalizumab also proved to be effective in patients suffering from idiopathic nonhistaminergic acquired angioedema (InH-AAE) in a preliminary case series. This led the investigators to hypothesize that InH-AAE may actually be an IgE-mediated disease, sharing the pathogenesis with CSU (Brunetta et al. 2018).

In patients who are refractory to omalizumab, along with reconsideration of alternative diagnoses from CSU, it is recommended that ciclosporin A is added to treatment. Ciclosporin is an immunosuppressant drug whose main mechanism is the inhibition of calcineurin in T cells. However, it has long been known to impede histamine release in mast cells and basophils (Cirillo et al. 1990; Stellato et al. 1992). Ciclosporin has been proven to be an effective drug for the treatment of CSU by two randomized controlled clinical trials, however, with low number of patients treated, and with short periods of treatment and observation after the interruption of therapy (Grattan et al. 2000; Vena et al. 2006).

Moreover, its use is limited by the severe side effects of hypertension and renal injury, which are dose-dependent and require monthly controls (Kulthanan et al. 2018). A daily ciclosporin dose of 3–3.5 mg/kg has obtained a success rate of 70–80%, while higher doses (4–4.5 mg/kg) are usually avoided because of higher risks of toxicity (Kaplan 2019). A recent metanalysis established the efficacy of cyclosporin with respect to placebo along with its mixed safety profile, with the common occurrence of side effects requiring interruption of treatment or reduction of the dosage (Kulthanan et al. 2018).

In patients in whom antihistamines, omalizumab and cyclosporin failed, a number of other medications have been used with variable success. These include leukotriene receptor antagonists, mycophenolate mofetil, methotrexate and hydroxicloroquine (Rutkowski and Grattan 2017). Guidelines do not discard completely this off-label approaches, which may be useful in individual and well-selected patients, but they instruct the physician to adopt a certain degree of caution due to the very low level of evidence which supports them (Zuberbier et al. 2018).

Biomarkers of Response to Treatment

Nowadays predicting the efficacy of a therapeutical scheme before prescribing the drug, seems pivotal to reach remission, improve the health of the patients and avoid waste. Several studies tried to identify and cluster groups of patients by clinical efficacy to a defined drug; nonetheless, foreseeing the response remains an unmet need in CSU treatment. In the table below are listed the main biomarkers described by the recent evidence (Table 5).

Table 5 Biomarkers with a potential prediction on drug treatment

Biomarker	Antihistamines	Omalizumab	Cyclosporine
Resistance			
Clinical	Hispanic	None	None
	Atopic asthma		
	Rhinosinusitis		
	Hypertension		
	Thyroid diseases		
	High UAS7		
	Longer duration of wheals		
Molecular	↑ C5a	BHRA +	None
	↑ IL-6	ASST +	
	↑ D-dimer	Low IgE levels	
	ASST +	CD203c up-regulation basophils	
Response			
Clinical	None	None	Short duration of CSU
			High initial severity
Molecular	↑ LCN2	BHRA -	BHRA +
	↑ Clusterin	ASST -	D-dimer
		Lack of CD203c basophils	
		High IgE levels	
		High FCεRI	
Increased relapse			
Clinical	None	High UAS7 at baseline	None
		Low UAS7 AAC	
Molecular	None	None	None

LCN2 Serum Lipocalin-2, *BHRA* Basophil histamine release assay, *ASST* Autologous serum skin test, *AAC* Area above the curve

6.3 Investigational Therapies

While existing pharmacological measures are effective in the majority of patients, they do not offer a long-lasting remission of symptoms after discontinuation of treatment. Moreover, they are not focused upon pathogenetic subsets within the disorder, but rather tackle CSU in a standardized manner.

On the contrary, the emerging approach of tailored treatment aims at providing the appropriate drug for each patient. This has become feasible due to an improved knowledge of CSU pathogenesis and biomarkers of disease. Currently, several drugs are under clinical and preclinical development for chronic urticaria.

6.3.1 Anti-IgE Humanized Monoclonal Antibodies

Of the drugs currently under investigation, the following two are certainly those with the greatest expectations in CSU. These are the anti-IgE humanized monoclonal antibodies quilizumab and ligelizumab.

Quilizumab targets membrane bound IgEs on IgE-switched B lymphocytes and plasma cells. It was found to reduce levels of total and specific IgEs in serum in patients with asthma and CSU (Harris et al. 2016a). However, in two randomized trials conducted in asthma and CSU, it was unable to provide any clinical benefit compared respectively to standard therapy and placebo (Harris et al. 2016a, b).

Ligelizumab mechanism of action is instead closer to omalizumab, as it equally binds soluble IgEs (Kocatürk et al. 2017). However, ligelizumab appears to be six to nine-fold more powerful than omalizumab. Furthermore, it shows a more prolonged suppression of IgE levels in serum (Kocatürk et al. 2017). This may be due to a different functional profile of the two drugs (Gasser et al. 2020). Indeed, not only does ligelizumab neutralize serum IgEs with increased

affinity, but it also appears to inhibit Ige production (Gasser et al. 2020). According to a recent study, ligelizumab may be able to downregulate IgE production by binding the CD23:IgE complex on the surface of B-cells, a feature which has not been shown with omalizumab (Gasser et al. 2020).

In a phase IIb randomized controlled trial which was recently published, 382 patients were either administered omalizumab, ligelizumab or placebo with varying doses and the response on weekly urticaria activity (with a focus on complete control of hives) was compared (Maurer et al. 2019). The primary endpoint of the study (complete control of hives) was assessed after 12 weeks of treatment. The study successfully determined a dose-response curve for ligelizumab and a statistically significant improvement in symptoms control with respect to omalizumab (complete hives response in 51% of patients treated with 72 mg ligelizumab with respect to 26% of patients who received 300 mg omalizumab) (Maurer et al. 2019). As the authors of the trial observed, the low percentage of patients who responded to omalizumab is puzzling and inconsistent with previous literature (Maurer et al. 2019). This has been interpreted as a consequence of patients selections criteria. Dose-limiting side effects were not observed, with generally no patients reporting anaphylaxis (Maurer et al. 2019).

6.3.2 Blockade of IL-1

Due to the efficacy of IL-1 blockade in autoinflammatory syndromes such as CAPS and Schnitzler's syndrome, along with the evidence of effect in some patients with physical urticarias, anti-IL-1 drugs have also been investigated in CSU (Bodar et al. 2009; Krause et al. 2012; Lenormand and Lipsker 2012). A phase II trial was conducted on the efficacy of canakinumab compared to placebo by the University of Zurich but results haven't been published yet (although the study was scheduled to end several years ago) (Fig. 3).

6.3.3 DARPins

A different and novel group of drugs is that of designed ankyrin repeat proteins (DARPins). These are small molecules, engineered to mimic antibodies binding capabilities, which can be administered orally (Kocatürk and Zuberbier 2018). Two of these were able to inhibit the binding of IgEs to their mast cells receptors and consequently block their activation (Kim et al. 2012). Unfortunately, they haven't reached yet a clinical stage of experimentation (Fig. 3).

6.3.4 SYK Inhibitors

In mast cells, spleen tyrosine kinase (SYK) plays an important role in intracellular signalling. It leads to a cascade of events ultimately causing release of histamine, prostaglandins and other mediators. The development of a topical formulation of a SYK inhibitor (GSK2646264) is currently being studied clinically in healthy controls and patients with CSU (Fig. 3) (Ramirez Molina et al. 2019; Barker et al. 2018).

6.3.5 BTK Inhibitors

A mechanistically similar target of future therapies may be Bruton's tyrosine kinase. Involved in B cell signalling and relevant to the production of IgEs, the inhibition of BTK yielded encouraging results in a study investigating the efficacy of oral ibrutinib (a BTK inhibitor) on mast cells and basophils activation (Dispenza et al. 2018; Herman et al. 2018). A phase II trial is now being conducted on patients with CSU for a different oral BTK inhibitor, fenebrutinib, in order to understand its safety and efficacy (Fig. 3).

6.3.6 Anti-Prostaglandin

CRTH2, a PGD2 receptor, was observed to be over-expressed by eosinophils in CSU patients (Yahara et al. 2010). An oral antagonist of CRTH2, AZD1981, was therefore studied in patients with CSU and H1-antihistamines refractoriness (Oliver et al. 2019). Interestingly, the short trial (4 weeks, placebo-controlled) showed benefit especially in terms of reduced itching, rather than hives extension. The drug was well tolerated and, at least in some aspects, more effective than placebo. Although not yet investigated in CSU, fevipiprant, a drug acting similarly to AZD1981 (a CRTH2 antagonist), has been

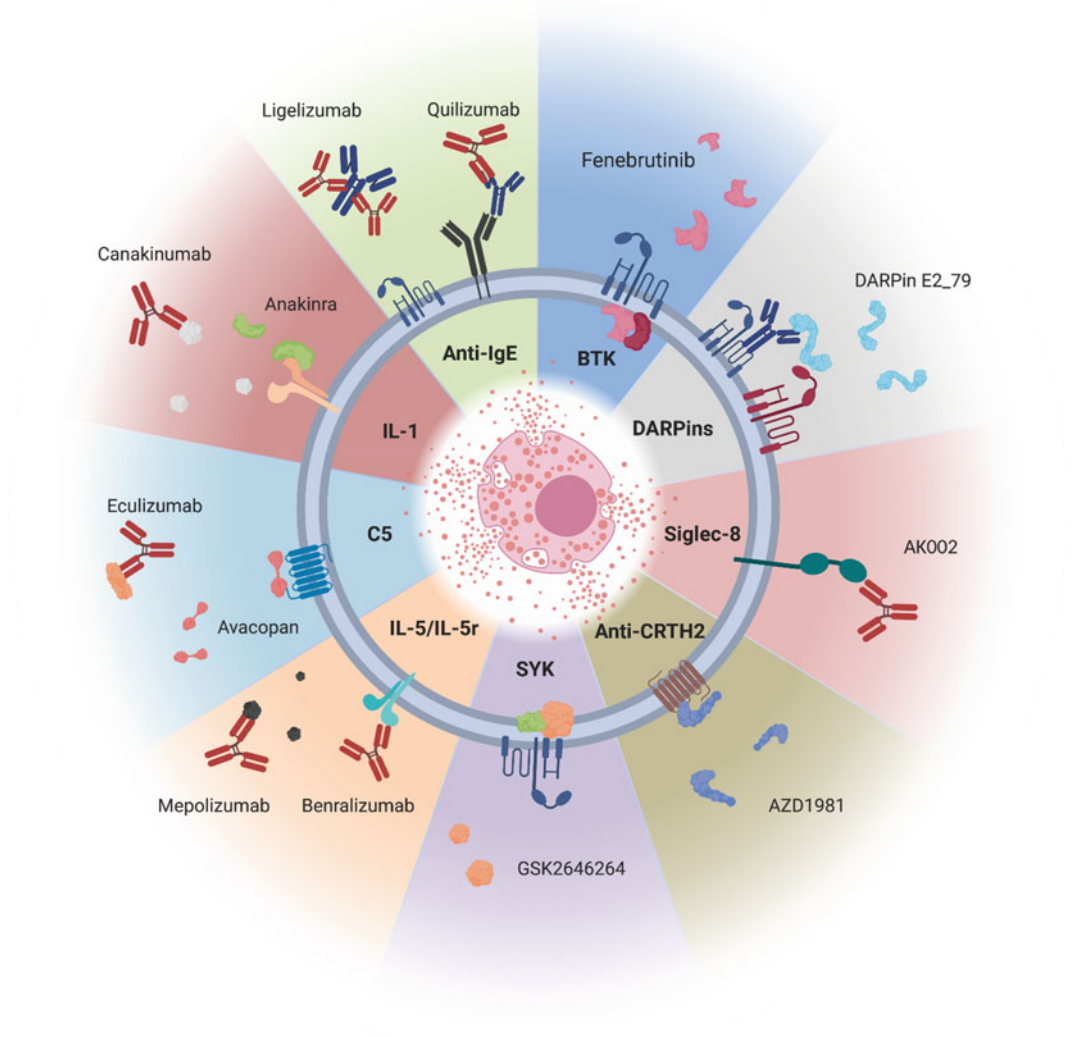

Fig. 3 Investigational therapies in CSU
Each segment represents a distinct pathway involved in the activation of mast cells (centre). Molecular mechanisms are represented on the outer part of the figure, as well as drugs studied to block them (Grey circle: cellular membrane; BTK: Bruton's tyrosine kinase; SYK: spleen tyrosine kinase)

extensively studied in asthma with important preliminary success, especially in severe eosinophilic asthma (Fig. 3) (White et al. 2018).

6.3.7 Anti-Complement Fragments

As described by several studies, complement binding plays a crucial role in enhancing the activating effects of IgG autoantibodies targeting mast cells IgE receptors (Fiebiger et al. 1995). In particular, C5 fragments have been postulated to bind mast cells C5a receptors leading to their activation (Kikuchi and Kaplan 2002). Eculizumab is a monoclonal antibody targeting C5, which has proven effective in paroxysmal nocturnal hemoglobinuria and atypical hemolytic-uremic syndrome. It would be of

great interest to evaluate the safety and efficacy of eculizumab in CSU (Kocatürk et al. 2017). Besides, a molecule targeting C5a receptor was recently developed and tested with preliminary success in patients with granulomatosis with polyangiitis (previously known as Wegener's granulomatosis, a vasculitis part of the group of ANCA-associated vasculitides) (Jayne et al. 2017; Tesar and Hruskova 2018). This molecule, whose name is avacopan, should equally be studied in CSU, where it may provide an additional clinical benefit in patients refractory to other treatments (Fig. 3).

6.3.8 Anti-IL-5 and IL-5 Receptors

Eventually, monoclonal antibodies targeting interleukin 5 and its receptor (respectively mepolizumab and benralizumab) may be effective in CSU, at least according to those who place eosinophils at the centre of urticarial pathogenesis (Kocatürk et al. 2017). This theory has gained popularity after a case was reported in which mepolizumab caused complete remission of CSU refractory to other treatments in a patient with concurrent severe uncontrolled asthma (Magerl et al. 2018). Currently, a phase I study of mepolizumab is undergoing in patients with CSU (Fig. 3) (Kocatürk and Zuberbier 2018). Recently, a non-randomized trial on 12 patients was published which evaluated the response to benralizumab in patients unresponsive to antihistamines (Bernstein et al. 2020). Patients were first administered placebo and subsequently three monthly doses of benralizumab (30 mg). The primary endpoint was the change in UAS7 after 20 weeks, which was found to be highly statistically significant (−15.7 points, 95% CI: −6.6 to −24.8, $p < 0.001$) (Bernstein et al. 2020). However, due to the small size of the patient group and the absence of randomization or even a control group treated with standard of care (omalizumab), it is difficult to infer any reliable information on benralizumab efficacy from this preliminary data.

6.3.9 Anti Sialic Acid-Binding Immunoglobulin-like Lectins (Siglecs)

The expression of Sialic acid-binding immunoglobulin-like lectins (Siglecs), a family receptors member of type I lectin, on human leukocytes is well demonstrated. The function of Siglecs in the human immune system is various, with inhibitory and activatory function depending on the cells expressing them (Varchetta et al. 2012). In particular, Siglec-8 is selectively expressed on human eosinophils, basophils and mast cells (Crocker et al. 2007). Its activation brings eosinophils to apoptosis and mast cells to inhibition of response (Nutku et al. 2003). For this reason, an anti Siglec-8 receptor was synthetized, AK002. Treatment of healthy subjects showed a rapidly depletion in blood eosinophils even after the single dose (Rasmussen et al. 2018). An open-label, phase 2a, pilot study showed how almost 92% of CSU patients naïve to omalizumab and 36% omalizumab-refractory obtained a complete remission (Fig. 3).

7 Prognosis

More than 80% of cases of acute urticaria don't progress beyond 6 weeks (Antia et al. 2018; Zuberbier et al. 1996; Aoki et al. 1994). In a study conducted on children, the rate of acute urticaria becoming recurrent or turning into chronic urticaria was estimated at about 30% (Mortureux et al. 1998). For what concerns the duration of chronic urticaria, different studies have provided variable results. A rate of 3-year remission of 32%, a 1-year remission rate of 47% and a 55% 1-year remission rate were all described by different authors (Champion et al. 1969; Quaranta et al. 1989; Kozel et al. 2001). 5-year remission rates have been observed to be 29% in adults and 67.7% in children (van der Valk et al. 2002; Chansakulporn et al. 2014).

In order to assess severity of disease and quality of life in chronic spontaneous urticaria, several tools have been developed. Among these, Chronic Urticaria Quality of Life Questionnaire (CU-Q20L) focuses on health-related quality of life, instead, the Urticaria Severity Score (USS) evaluates quality of life and need for medications. The most used in the clinical setting is the urticaria activity score-7 (UAS-7), which evaluates severity of the disease (Antia et al. 2018) by the calculation of a weekly score based upon daily itching (0–3 points) and the number of wheals (0–3 points) (Mlynek et al. 2013; Mathias et al. 2010). When the total weekly score sums up to less than 7, disease is well controlled. With higher scores, disease is progressively less controlled.

Studies performed on patients with CSU, in order to assess their quality of life and satisfaction with treatment, have invariably brought forward worrying results. From an online survey conducted in Germany, it emerged that approximately half of the more than 17,000 participants felt their symptoms were uncontrolled (Maurer et al. 2016). A subsequent observational study, conducted on patients with CSU who had persistence of symptoms despite treatment, demonstrated that more than half of the patients had moderate-to-severe disease activity based upon the UAS-7 (Maurer et al. 2017b). Unfortunately, according to another recent study, it appears that a large percentage of patients is undertreated due to lack of adherence to guidelines. In a cohort of patients with CSU refractory to antihistamines, only a minority was informed about the possibility of omalizumab treatment (Maurer et al. 2017a).

Eventually, it should be kept in mind how CSU, although not a life-threatening condition, is a chronic disorder carrying an important burden on patients health and quality of life. While treatment is not always effective, it may still elicit adverse reactions. The ineffectiveness of treatment may be due to the standardized "one-size-fits-all" stepwise approach which is adopted in CSU. Indeed, the possibility of adopting customized therapies for individual patients is not presently available in CSU.

However, the implementation of a laboratory diagnostics (a set of molecular biomarkers) capable of distinguishing subsets of patients with different mechanisms of disease is the contemporary goal of the most respected investigators. Concurrently, an impressive number of novel medications are being tested for future use in CSU. Some of these, due to their specific targets, may only be used in specific cases. All things considered, it seems to be a matter of time before the revolution of precision medicine fully takes place in the setting of urticaria.

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