

REVIEW ARTICLE

Factors linked to disease severity and time to remission in patients with chronic spontaneous urticaria

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Abstract

Biomarkers useful for the evaluation and management of patients with chronic spontaneous urticaria (CSU) are not currently available. A review of various clinical and laboratory markers that have been studied to assess their value for determining the severity or predicting the evolution of disease in adult patients with CSU was carried out. A search of the medical literature on PubMed and MEDLINE including the terms urticaria, chronic urticaria, chronic idiopathic urticaria, CSU, severity, prognosis and treatment was performed. Based on our review of the literature, among the clinical markers studied, higher age at onset, being female, long disease duration and aspirin/NSAID hypersensitivity may be linked to both severe CSU and a long time to spontaneous remission. In addition, a positive autologous serum skin test (ASST) may be associated with severe CSU, and comorbidity of inducible urticaria and concomitant recurrent angio-oedema may be linked to longer CSU duration. Potential biomarkers of CSU severity and/or duration include basophil numbers and susceptibility to activation, inflammatory markers, markers of activation of the extrinsic coagulation pathway, immunoglobulin E and vitamin D. Although the described markers are promising, further studies on representative and well-characterized patient populations are needed to determine the value of these clinical and biological markers for predicting the severity and course of disease in patients with CSU.

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Conflicts of interest

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Introduction

Chronic spontaneous urticaria (CSU), also sometimes called chronic idiopathic urticaria, is a highly prevalent cutaneous disease and a frequent cause for medical consultation. Reported lifetime prevalence rates are estimated to be as high as 8–10% of the population¹ with a point prevalence of 0.6%.² In many patients, the disease results in significantly impaired quality of life.³ This is largely due to the fact that CSU in many patients is severe, with high disease activity, the occurrence of both weals and angio-oedema, high impact on sleep and daytime activities including work, and/or insufficient responses to standard treatment. In addition to disease severity, the unpredictability of CSU and its course are a major cause of concern for patients.

Several studies have investigated potential markers, clinical and laboratory ones, of CSU severity and course. This article discusses the results of our review of these studies and provides relevant information on which clinical factors and complementary biomarkers may be helpful to ascertain the severity of CSU and for predicting its course, i.e. the time to spontaneous remission in a given patient.

Methods

A search of the medical literature was performed on PubMed and MEDLINE, including the terms urticaria, chronic urticaria, chronic idiopathic urticaria, CSU, severity, prognosis and treatment. All reference types were included in the search, and the

results of published studies identified as relevant for CSU in adults were assessed for their evidence levels by the use of the GRADE categories (Table 1).⁴

Results

Clinical markers of severity and time to remission

Our search of the medical literature identified studies on various clinical features of CSU linked to disease severity and time to spontaneous remission. The following clinical parameters have been investigated for their association with high CSU severity (as defined by high disease activity, the occurrence of both weals and angio-oedema, high impact on quality of life including on sleep and daytime activities such as work, and/or insufficient response to standard treatment) and/or a long time until spontaneous remission: (i) age, (ii) gender, (iii) disease duration, (iv) occurrence of recurrent angio-oedema, (v) comorbidity of inducible urticaria, (vi) comorbidity of hypertension and metabolic syndrome, (vii) comorbidity of aspirin/NSAID hypersensitivity, (viii) lack of response to treatment and (ix) positive autologous serum skin test (ASST). As a summary, clinical markers of severity and time to remission of CSU are presented in Table 2.

Age Most patients with CSU are females between 20 and 59 years old.⁵ We found very few studies on the link between age and disease severity. In one study, age significantly predicted quality-of-life impairment of patients with CSU in the domains functioning, sleep, itching/embarrassment and swelling/eating assessed with the disease-specific Quality of Life (QoL) instrument CU-Q2oL (evidence level: III).⁶ Younger subjects were more affected on functioning and itching/embarrassment, whereas older patients were more severely affected on sleep and swelling/eating. For chronic cold urticaria, Katsarou-Katsari *et al.*⁷ found that the disease was less severe if patients developed the condition after 30 years of age.

The only study we found on the link between age and prognosis in patients with CSU reported that improvement rates are significantly higher in patients <19 years old as compared to adults.⁸

Gender Adult patients with CSU are predominantly female, but little is known about the differences of disease severity and duration in male and female patients with CSU. With respect to the severity of the disease, one study found that gender significantly predicts QoL impairment in the CU-Q2oL domains itching/embarrassment and limits looks, with women more severely affected in both domains (evidence level: III).⁶ Being female may also be associated with a longer time to remission according to Gregoriou *et al.*⁹ (evidence level: III).

The observed increased prevalence and severity in females has led to the speculation on a possible influence of sex hormones on CSU, but the available data for this relationship are scarce. In that regard, it has been reported that CU may be associated with endocrinopathies, menstrual cycle, pregnancy, menopause and hormonal contraceptives or hormone replacement therapy. Therefore, it is proposed that the influence of fluctuations in the hormonal milieu and altered sex hormone expression on the triggering, maintenance or aggravation of urticaria should be taken into account.

Oestradiol enhances IgE-mediated release of b-hexosaminidase from RBL-2H3, BMMC and HMC-1 mast cell lines and enhances IgE-mediated histamine release from rat uterine mast cells (reviewed in reference 10). Also, an autoimmune progesterone dermatitis or progesterone hypersensitivity, characterized by a dermatitis flare related to premenstrual or exogenous progesterone exposure, has been described.^{11,12}

Dehydroepiandrosterone (DHEA) and its sulphate derivative (DHEA-S) are weak androgens produced by the adrenal gland that serves as the primary precursor in the biosynthesis of androgens and oestrogens. Kasperska-Zajak *et al.*^{13,14} observed a decreased serum concentration of DHEA-S in patients with chronic urticaria, and DHEA-S levels were significantly lower in symptomatic patients as compared to those with disease remission. Currently, it is not clear whether a neuroendocrine-immune dysfunction due to psychological stress is a primary aetiological factor of CU or it is indeed an epiphenomenon, and therefore, no support for DHEA supplementation as adjuvant therapy for the disease can be recommended.

In a cross-sectional study that included interviewing 200 women with CU, it was observed that the disease occurred more often after the puberty and it worsened in four of 16 women during pregnancy, whereas hormonal contraception exacerbated CSU in 10%.¹⁵ The authors concluded that sex hormones act as a trigger in only a small subset of women with CU. CSU exacerbated by oestrogens should be distinguished from hereditary angio-oedema type III, which is oestrogen-dependent, and is associated with normal levels of C1 inhibitor.¹⁶

In children with CSU, a study by Chansakulporn *et al.*¹⁷ did not demonstrate any effect of gender on remission rates. This is in contrast to previous studies: the retrospective study of Harris *et al.*¹⁸ demonstrated that among 52 children with CSU, 37% were free of symptoms after 1 year and girls had a higher rate of

Table 1 GRADE system for classification of evidence⁴

Category of evidence	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Table 2 Clinical markers of severity and prognosis in adult patients with chronic spontaneous urticaria

Marker	Link to severity	Category of evidence† (ref)	Link to time to remission	Category of evidence† (ref)
Higher age	+ and –	III (6)	+	III (8)
Female gender	+	III (6)	+	III (9)
Long disease duration	+	III (17)	+	III (7,8)
Concomitant angio-oedema	n.a.		+	III (9,17,20–22)
			Ø	III (23)
Comorbidity of inducible urticaria	Unknown		+	III (3,8,24)
Comorbidity of hypertension	Unknown		+	III (26)
Comorbidity of metabolic syndrome	±	III (28)	Unknown	
Comorbidity of ASA/NSAID hypersensitivity	±	III (30,31)	±	Ib (30,31)
Lack of response to the treatment	n.a.		Unknown	
Positive ASST	+	Ib (36,78–83)	+	Ib (36)
	Ø	III (14,84,85)	Ø	III (25)

†Highest level of evidence of supporting study according to the GRADE system.⁴

n.a., not applicable because marker is a defining feature of severe CSU; (ref), reference(s); +, positive correlation; –, negative correlation; Ø, no correlation.

resolution than boys. Sahiner *et al.*¹⁹ reported that the prognosis was unfavourable in girls older than 10 years.

Disease duration Epidemiologic studies have established that in up to 50% of patients with CSU a remission occurs in 3 months, whereas in about 80% it will last 12 months, and in 11% the urticaria will persist for more than 5 years.² But what is known about the relationship between disease duration and disease severity? Several studies have indicated that the duration and disease severity of CSU are associated. Toubi *et al.*²⁰ observed that longer disease duration and positive ASST were present in patients with more severe CU (evidence level: III). Disease duration was also correlated with angio-oedema and the presence of antithyroid antibodies.

The association between thyroid autoimmunity and CSU has been widely recognized. However, a correlation between antithyroid antibody titres in the serum and the severity of urticaria is not clearly established, although one study observed that prehospitalization duration of CSU correlated with the serum concentration of antibodies to thyroid peroxidase.²¹

What is known about the relationship between disease duration and time to resolution? According to Gregoriou *et al.*,⁹ duration of urticaria at the initial evaluation is associated with the time to remission. The improvement rate of patients with short disease duration (<1 year) is significantly higher than that of patients with long disease duration (>1 year).⁸ This appears to be true also for children as reported by Eser and co-workers who prospectively followed a total of 52 children with CSU over a period of 3 years. At 12 and 36 months, 33% and 48% of them showed remission, respectively, and the mean duration of disease at the first visit in patients who did not show remission after 3 years was higher than in those who did.²² In contrast, a previous study by Chansakulporn *et al.*¹⁷ did not find duration of disease or other demographic variables to predict remission of CSU in children.

Occurrence of weals and angio-oedema Investigations from different centres agree that patients with CSU who show concomitant angio-oedema show longer disease duration and a longer time to remission (evidence level: Ia),^{9,20,23–25} although one study reported that CSU patients with and without angio-oedema did not differ significantly in their duration of disease (evidence level = III).²⁶

Champion *et al.*,²⁵ for example, reported that 70% of patients with weals and angio-oedema still had CSU 1 year after the onset of disease, whereas this was the case in only 48% of patients who had weals but not angio-oedema. Similar results were reported by Toubi *et al.*²⁰: CSU patients with weals still had CSU 2 years after the onset of disease in 64% and 43% of cases associated with angio-oedema and not associated with angio-oedema, respectively. In addition, several studies found that CSU patients with angio-oedema but no weals had an even less favourable prognosis. Kozel *et al.*,²⁷ for example, showed that CSU with angio-oedema and without weals persists for more than 1 year in 80% of patients.

Comorbidity of inducible urticaria The prevalence of CSU occurring in combination with physical urticaria (most commonly symptomatic dermographism and delayed pressure urticaria) or other inducible forms of urticaria is high, from 10% to 50%.²⁸ Longer disease duration has been reported in patients with CSU who have comorbid physical urticaria (evidence level: III).^{3,8,27} Patients with CSU and physical urticaria, according to Kozel *et al.*,²⁷ showed remission rates of only 21% after 1 year, as compared to 47% in patients with isolated CSU.

Comorbidity of hypertension and metabolic syndrome Nebiolo *et al.*²⁹ observed and reported that arterial hypertension is associated with extended duration of CSU (evidence level: IIb).

Furthermore, Chang *et al.*³⁰ recently proposed that CSU is associated with an increased future risk of hypertension.

Metabolic syndrome (MS) is defined as the combination of central obesity, dyslipidaemia, elevated blood pressure and increased fasting plasma glucose. According to Ye *et al.*,³¹ the prevalence of MS is significantly greater in patients with CSU than in healthy controls and predicts uncontrolled disease. The presence of MS, together with a high urticaria activity score, is an independent predictor of uncontrolled CU. Patients with CSU and MS are older and have increased inflammatory markers such as serum eosinophil cationic protein, TNF- α and complement, and a decreased rate of ASST positivity.

Comorbidity of aspirin (ASA) and NSAID hypersensitivity The relation between ASA/NSAID hypersensitivity and urticaria has been motive of interest to physicians for a long time. ASA/NSAIDs can induce acute urticaria (NSAID-induced U/AE/anaphylaxis).³² Also, a substantial proportion, up to 40%, of patients with CSU experience exacerbations when exposed to ASA/NSAIDs. CSU with NSAID hypersensitivity is termed ASA/NSAID-exacerbated cutaneous disease (AECED).³³

We have observed that patients with AECED experience more severe disease, with longer duration, increased frequency of atopy and laryngeal angio-oedema, when compared with patients with CSU who are tolerant to NSAIDs.³³ Shin *et al.*³⁴ observed that patients with ASA-induced urticaria have a more severe and chronic disease.

Lack of response to treatment Current international guidelines recommend second-generation, non-sedating antihistamines as the first line of treatment for CSU.³⁵ Patients who do not respond to conventional doses of antihistamines should receive increased doses, up to four times the approved dose, to improve the possibility of control. However, it has been observed that up to 50% of patients will not gain symptom improvement after receiving antihistamines.³⁶ In such patients, alternative medications are recommended, including omalizumab, cyclosporin A and a number of other drugs with less evidence of efficacy. Long-term use of corticosteroids is discouraged due to safety concerns, while they can be used exclusively for short periods of time during disease exacerbations.

Insufficient response to treatment is a defining feature of severe CSU. In general, there is scarce information on the factors that may predict a favourable therapeutic response. In a recent study, failure of patients with CSU to respond to antihistamine treatment was associated with other clinical indicators of severity.³⁷ Another investigation showed that antihistamine-resistant CU shows increased complement C5a fraction, higher disease activity, longer duration of weals and higher positivity of the ASST.³⁸ ASST and basophil activation test (BAT) positivity are associated with a poor response to antihistamine treatment in patients with CU.³⁹ Furthermore, in a study that included 91

patients, Asero proposed that elevated D-dimer plasma levels should be considered a marker of antihistamine-resistant CU.⁴⁰

What is known about response to treatment and time to resolution? We found no published evidence that failure to respond to treatment in adult patients with CSU is linked to long disease duration. In children with CSU, remission rates of patients who respond to standard dosed antihistamine treatment are reportedly higher than those of patients who require high-dose antihistamine or combination medications, indicating that urticaria controlled by a standard dose of antihistamine may predict a shorter time to remission in the paediatric CSU population.²²

Recent studies have investigated possible markers of response to omalizumab. According to Gericke *et al.*,⁴¹ there are significant correlations between a positive basophil histamine release assay (BHRA) and ASST and the time to symptom relief with omalizumab. The fact that a positive BHRA is predictive of a slow response to omalizumab suggests that omalizumab works via reducing Fc ϵ RI expression in these patients. Palacios *et al.*⁴² reported that the lack of basophil CD203c-upregulating activity in the serum of patients with CU correlates with the clinical response to omalizumab.

Patients with CSU with positive BAT results respond better to cyclosporine treatment than those with negative BAT results.⁴³ This finding was confirmed in Iqbal's paper which reported that in patients treated with cyclosporine, a positive BHRA indicated a higher probability of response.⁴⁴ Furthermore, shorter duration of the disease and higher initial severity predict a successful response to treatment with cyclosporine.⁴⁵

Baseline D-dimer levels show a highly significant negative correlation with the response to cyclosporine.⁴⁶ Other authors have postulated that baseline D-dimer is a good marker of disease activity in most patients with CSU and may be useful to monitor the clinical response to cyclosporine treatment.⁴⁷

An imbalance in pro- and anti-inflammatory adipokines in patients with CU has been recently observed by Trinh *et al.*⁴⁸ The authors suggested that LCN2 could be a differential marker for disease activity and the clinical responses to antihistamine treatment in patients with CU.

Positive autologous serum skin test The ASST is a screening test for type II autoimmune urticaria, i.e. the expression of mast cell and basophil-activating IgG autoantibodies directed against the high-affinity IgE receptor. Several studies, but not all, support the notion that a positive ASST is linked to severe disease (Tables 2 and 3). Whether or not a positive ASST is linked to longer disease duration is much less clear, and there is only one adult CSU study that supports this as well as one that did not show a link (Tables 2 and 3).

Laboratory markers of severity and prognosis

Predictions of disease severity and duration based on the presence of clinical features may benefit from the use of

Table 3 Autologous serum skin test (ASST) as a biomarker of disease severity in chronic urticaria

Author (year) ^{Ref}	n	Remarks
Sabroe <i>et al.</i> (1999) ⁸⁴	107	Presence of autoantibodies against FcεRI or IgE correlated with more severe chronic urticaria
Nettis <i>et al.</i> (2002) ⁸¹	102	Higher incidence of angio-oedema in patients with positive ASST
Caproni <i>et al.</i> (2004) ⁸⁵	68	Patients with positive ASST showed more severe chronic urticaria
Kulthanan <i>et al.</i> (2006) ⁸²	85	No significant difference between patients with positive and negative ASST in regard to severity and duration of chronic urticaria
Staubach <i>et al.</i> (2006) ³⁹	56	Chronic urticaria in ASST-positive patients was of longer duration and required more antihistamine medication
George <i>et al.</i> (2008) ⁸³	100	Patients with positive ASST showed higher frequency and severity of urticarial attacks
Bèlot <i>et al.</i> (2010) ⁸⁶	74	Positivity of ASST is not associated with greater severity or resistance to treatment
Alaysin <i>et al.</i> (2011) ⁸⁷	69	Patients with positive ASST had significantly higher number of weals, with larger sizes, higher frequency of weals and higher disease activity scores
Vohra <i>et al.</i> (2011) ⁸⁸	100	ASST-positive patients had higher mean urticaria activity scores, frequent involvement of more body sites, throat angio-oedema and general symptoms
Chansakulporn <i>et al.</i> (2014) ¹⁷	92	In children with chronic urticaria a positive ASST result did not determine a poorer prognosis
Ye <i>et al.</i> (2016) ⁸⁹	75	ASST positivity is a significant predictor of better response to treatment

complementary laboratory markers. Indeed, several blood markers have been investigated for their link to CSU features, mostly disease activity and response to treatment. Little is known about which blood markers predict high disease severity and duration. Based on the literature, the following markers deserve further exploration for their value as biomarkers of CSU severity and/or duration: basophils and basophil activation, inflammatory markers, markers of activation of the extrinsic coagulation pathway, immunoglobulin E and serum vitamin D.

Basophils and basophil activation Various abnormalities related to basophils and their functions have been described in patients with CSU. First, blood basopenia reportedly correlates with disease activity as assessed by means of the urticaria activity score.^{49,50} Basopenia is related to the recruitment of basophils to lesional skin sites.⁵¹ Systemic corticosteroid therapy, which leads to an increase in blood basophil numbers and reduces skin symptoms in CSU, is known to inhibit basophil recruitment to the skin.^{50,52,53}

Second, abnormal basophil functions are present. Vonakis *et al.*⁵⁴ observed altered blood basophil phenotypes in CU. A reduced IgE-receptor-mediated histamine release indicating a specific defect in the FcεRI pathway has been described.^{55–58} Patients with CSU with a basophil responder phenotype to anti-IgE may have longer disease duration, higher frequency of visits to the emergency department and significantly higher severity of itch.⁵⁹

The expression of CD203c on basophils is a well-known activation marker that can be used as a potential marker of severe urticaria as it is increased when compared with non-severe urticaria and normal controls. In one study, the mean basophil CD203c expression was significantly higher in patients with severe urticaria.⁶⁰ In CSU subjects who enter into remission basophils shift towards normalization of basophil IgE-receptor-mediated histamine release and correction of basopenia.^{56,61} Taking together the mentioned observations, basophil numbers

and functions should be further explored for their link to defining features of severe CSU as well as long disease duration.

Inflammatory markers It has been repeatedly proposed that CSU is a chronic inflammatory condition with systemic manifestations. This is supported by several studies on how inflammatory blood markers in patients with CSU are associated with the course of the disease. For example, C-reactive protein (CRP) is increased in patients with CSU, especially in patients with positive ASST, and increased CRP levels reportedly correlate with disease activity.^{62–66}

Other inflammatory markers that have been claimed to be elevated and linked to disease activity include IL-6,⁶⁵ IL-18,⁶⁶ complements C3 and C4,⁶⁷ vascular endothelial growth factor (VEGF),⁶⁸ B-cell-activating factor (BAFF)⁶⁹ and matrix metalloproteinase-9 (MMP-9).^{66,70} Few studies have tried to correlate the blood levels of inflammatory parameters with the clinical activity in CU. For example, Ye *et al.*³¹ observed a correlation between uncontrolled CU and levels of C3, TNF-α and eosinophil cationic protein, whereas other studies reported that IL-6 and CRP correlate with clinical activity.^{63,64}

Elevations of these markers of inflammation in the blood of patients with CSU may correlate with disease severity and course and should be explored for their value as predictors by multi-centre studies in representative and well-characterized CSU populations.

Markers of activation of the extrinsic coagulation pathway Asero *et al.*^{71,72} observed an increase in plasmatic markers of thrombin generation and fibrinolysis in patients with severe CSU, possibly as a consequence of tissue factor expression by activated eosinophils.⁷³ This observation has been confirmed in other studies.⁷⁴ Along the same lines, Rabelo-Filardi *et al.*²³ observed an increase in prothrombin fragment 1 + 2, D-dimer and CRP in patients with CSU and proposed that these markers correlate with disease severity. The activation of coagulation/

Table 4 Clinical correlates of biomarkers in chronic spontaneous urticaria

Biomarker	Clinical implication
Female gender	Higher impairment of quality of life, longer time to remission
Disease duration	Correlated with disease severity, time to resolution, presence of angio-oedema and antithyroid antibodies
Concomitant angio-oedema	Correlated with poorer prognosis, longer disease duration and longer time to remission
Comorbid inducible urticaria	Correlated with longer disease duration and lower remission rates
Hypertension	Longer disease duration
Metabolic syndrome	Lack of control
ASA/NSAID hypersensitivity	Higher severity
ASST positivity	Correlated with disease severity
Lack of response to antihistamines	Higher severity and lower remission rates
Basophil numbers and activation	Correlated with disease activity, severity and longer duration
Inflammatory markers	Correlated with disease activity and severity?
Markers of activation of the extrinsic coagulation	Correlated with disease activity and severity
Immunoglobulin E	Correlated with disease activity and severity?
Serum vitamin D levels	Correlated with disease activity and severity?

fibrinolysis in patients with CU parallels disease activity^{72,74} and decreases during remission.^{72,75} These findings should prompt further studies that aim to investigate the predictive value of these markers for CSU severity and prognosis.

Immunoglobulin E (IgE) A recent study observed that 93% of patients with increased total IgE had moderate-to-severe CSU, vs. 69% of patients with normal serum IgE, and the authors proposed that total serum IgE could be a potential marker for urticaria severity and duration.⁷⁶ This notion is supported by new findings that point to IgE-mediated autoimmunity as a cause of CSU in a subpopulation of patients. In that regard, highly cytotoxic IgE antibodies with polyreactivity to autoantigens including thyroid peroxidase (TPO) in the sera from patients with atopic dermatitis, which could induce mast cell activation, have been reported by Kim and Park.⁷⁷ IgE against TPO is a common feature of patients with CSU.

A relation of IgE and thyroid autoimmunity has been observed in CSU. One investigation found that 54% of patients with CSU expressed IgE antibodies against TPO.⁷⁸ This association was confirmed by Shin *et al.*³⁴ In that paper, levels of serum specific IgE to TPO were significantly higher in aspirin intolerant acute and chronic urticaria than in aspirin tolerant patients with urticaria.

Vitamin D Woo *et al.*⁷⁹ have observed that low serum vitamin D levels are associated with increased severity and duration of CU, and this observation has led to a proposal to utilize vitamin D as adjuvant therapy for CU.⁸⁰ Further studies are needed to explore the specificity and sensitivity of serum vitamin D levels for correlation with CSU severity and duration.

Conclusions

Several clinical features appear to be linked to disease severity and/or duration in patients with CSU. Among them, time since

onset of the disease, concomitant angio-oedema, comorbid inducible urticaria and ASST positivity appear to be the best candidates to be explored in further studies of their usefulness as predictive markers (Table 4). Such studies should be large-scale, multicentre and prospective and should ideally include measurements of possible biomarkers, especially markers of basophil numbers and activation, inflammatory markers, markers of activation of the extrinsic coagulation pathway, IgE and vitamin D.

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