Urticarial vasculitis differs from chronic spontaneous urticaria in time to diagnosis, clinical presentation and need for anti-inflammatory treatment: An international prospective UCARE study

Short title: Urticarial vasculitis versus chronic spontaneous urticaria: A UCARE study

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Abstract

Background:

Chronic spontaneous urticaria (CSU) and urticarial vasculitis (UV) share several clinical features including the occurrence of wheals. As of yet, the criteria for differentiating the two disorders are not clearly defined.

Objective:

Here, we aimed to identify differences, similarities and the likelihood for specific clinical features in UV versus CSU patients.

Methods:

Across 10 Urticaria Centers of Reference and Excellence (UCAREs), 106 patients with skin biopsy-confirmed UV and 126 CSU patients were prospectively recruited to complete a questionnaire on the clinical features, course, and response to treatment of their disease.

Results:

As compared to CSU, UV patients more often experienced post-inflammatory skin hyperpigmentation, wheals of ≥24h duration, eye inflammation, and fever (6.9, 4.0, 3.6, and 2.4 times, respectively). Clinical features that increased the risk for UV diagnosis when present at the onset of disease included wheals of ≥24h duration (7.3-fold), pain of the skin (7.0-fold), post-inflammatory hyperpigmentation (4.1-fold), and fatigue (3.1-fold). The diagnostic delay was markedly longer for normocomplementemic UV as compared to hypocomplementemic UV and CSU (21 vs 5 vs 6 months, respectively). Oral corticosteroids and omalizumab were the most effective treatments in UV and

CSU patients, respectively. UV patients showed a higher need for immunosuppressive and anti-inflammatory therapies than CSU patients.

Conclusions: Long wheal duration, skin pain and hyperpigmentation, and systemic symptoms point to UV rather than CSU as the underlying disease and should prompt further diagnostic work-up including a skin biopsy.

Highlights Box:

What is already known about this topic?

Chronic spontaneous urticaria (CSU) is the most common reason for recurrent wheals, but some patients develop them because they have urticarial vasculitis (UV), a more severe and difficult-to-treat condition. As of yet, the clinical criteria for differentiation between the two disorders are not well established.

What does this article add to our knowledge?

As compared to CSU, UV is associated with longer diagnostic delay (normocomplementemic form), post-inflammatory hyperpigmentation of the skin, wheals of ≥24h duration, systemic symptoms and higher need for immunosuppressive and anti-inflammatory therapies.

How does this study impact current management guidelines

Routine assessment of the skin and systemic symptoms we identified to be linked to UV will improve the diagnostic work-up of patients with recurrent wheals. This would shorten the diagnostic delay and allow for earlier appropriate treatment of UV.

Key words:

chronic spontaneous urticaria; urticarial vasculitis; diagnosis; criteria; Urticaria Centers of Reference and Excellence

Abbreviations:

BMI	Body Mass Index
CSU	Chronic spontaneous urticaria
HUV	Hypocomplementemic urticarial vasculitis
NUV	Normocomplementemic urticarial vasculitis
ORa	Odds Ratio
QoL	Quality of life
SD	Standard deviation
UCARE	Urticaria Center of Reference and Excellence
UV	Urticarial vasculitis

Data availability statement: All datasets generated for this study are available from the corresponding author upon reasonable request.

Introduction

Chronic urticarial rash is present in about 1-4% of the general population at one point of time.(1) Most patients with recurrent wheals have chronic urticaria, mostly chronic spontaneous urticaria (CSU). But up to 27% of patients initially diagnosed with CSU are later found to have urticarial vasculitis (UV), a rare, more severe and difficult-to-treat condition.(2, 3, 4, 5, 6)

CSU is a mast cell-driven disease characterized by the development of itchy wheals with a fleeting nature (usually resolving in <24h), angioedema or both for more than 6 weeks.(1, 7, 8, 9) Skin histopathology usually shows a mild infiltrate consisting of lymphocytes, macrophages, monocytes, eosinophils, basophils, and/ or neutrophils without signs of vasculitis.(7) IgE autoantibodies against autoallergens, e.g. IL-24, and IgG/IgM autoantibodies against IgE and FcεRI on mast cells and basophils are thought to be drivers of CSU pathogenesis.(10) These autoantibodies lead to mast cell activation and degranulation that results in the release of histamine and other pro-inflammatory mediators. Guideline-recommended treatments include 2nd-generation H1-antihistamines (standard dose or updosed), omalizumab, a monoclonal anti-IgE antibody, and cyclosporine.(7) UV is a primary differential diagnosis in a patient with CSU.(1, 7)

UV is defined by long lasting urticarial skin lesions combined with the histopathologic finding of leukocytoclastic vasculitis.(7) The reported incidence of UV is 0.5 per 100,000 person-years in the United States.(11) In addition to recurrent wheals, UV can present with severe systemic, organ-specific manifestations such as fever, joint, pulmonary, gastrointestinal, renal, ear, nose and eye involvement and neurological complaints.(6, 12, 13, 14) The pathogenesis of UV is poorly investigated

and understood. It includes the intravascular deposition of antigen-antibody complexes with activation of the complement system.(15) Based on blood complement levels, UV is divided into a more frequent normocomplementic subtype, i.e. normocomplementic urticarial vasculitis (NUV), in approx. 80% of UV patients, and hypocomplementemic subtypes (HUV).(2, 16, 17) HUV has a point prevalence of 9.5/million(18) and is more severe, with a higher frequency of systemic symptoms(17) and association with underlying diseases including infections, autoimmune disease and malignancies.(19) More than 50% of UV patients show a severe impairment of quality of life (QoL) associated with long disease duration, marked symptom burden, and a high need for therapy.(14)

Skin biopsy is the gold standard for distinguishing between UV and CSU, and histopathologic criteria have recently been developed.(20) However, skin biopsy is invasive and should only be performed in CSU patients with a strong clinical suspicion of UV. Therefore, reliable clinical criteria are needed to select patients for skin biopsy.

UV and CSU patients show differences as well as similarities in clinical features, laboratory markers, and response to treatment. For example, patients with UV have higher rates of concomitant autoimmune diseases, increased erythrocyte sedimentation rate, C-reactive protein and antinuclear antibody positivity than CSU patients.(21) The international urticaria guideline recommends the assessment of several clinical parameters for distinguishing between CSU and UV such as wheal duration and systemic signs and symptoms(7), but there is little scientific evidence to back these recommendations. In fact, up to 60% and 66% of CSU patients, respectively, were previously reported to have wheals of >24 h duration and systemic complaints.(21, 22, 23, 24, 25) More information on the clinical discrimination of UV

and CSU patients is needed, and direct comparisons between UV and CSU on the global level and in a sizeable cohort of patients are warranted.

In this international multicenter study, we aimed to assess differences and similarities in clinical features and response to treatment in patients with UV and CSU and to evaluate the risk for specific clinical features in UV patients versus CSU patients.

Methods

Study design

In this international, prospective, investigator-initiated observational (non-interventional) multicenter study, 106 UV and 126 CSU patients were recruited at 10 GA^{2}LEN Urticaria Centers of Reference and Excellence (UCAREs, https://ga2len-ucare.com (26)) in China, Ecuador, Brazil, Germany, Iran, Oman, Russia and Turkey (**Table E1**). The study was approved by the Charité – Universitätsmedizin Berlin ethics committee (Berlin, Germany; EA4/108/18) and by the ethics committees of the participating UCAREs, as required.

Patient population

We analyzed adult patients with chronic recurrent wheals who either had UV, as confirmed by histopathology (signs of leukocytoclastic vasculitis in lesional skin [**Figure E1A**]) or CSU (recurrence of wheals, angioedema, or both for >6 weeks, independent of a specific and definite trigger). Thirty-one of 114 CSU patients (including those with any clinical features of UV, e.g. wheals of >24 h duration and/or residual hyperpigmentation) underwent skin biopsy and did not have histopathological signs of vasculitis (**Figure E1B**). Twenty of 114 CSU patients had concomitant chronic inducible urticaria (10 symptomatic dermographism, 5 delayed pressure urticaria, 2 delayed pressure urticaria combined with cholinergic urticaria and symptomatic dermographism, 1 cholinergic urticaria combined with symptomatic dermographism, 1 solar urticaria and 1 contact urticaria). CSU patients with angioedema but without wheals and patients who could not be clearly categorized as UV or CSU were not included in the study. Complement levels were available for 74 UV patients, and

sixteen of them (21.6 %) had HUV. For inclusion, the patients had to be able to read, understand, and be willing to sign the informed consent form and abide with study procedures. All patients provided written and oral informed consent.

Study survey

A patient questionnaire was developed by H.B. and K. K. and circulated among the members of the UCARE project steering committee (A.G.A., M.G., M.Ma., Z.Z.) for revision. The final version (**Figure E2**) consisted of 25 questions, 3 and 22 of them with 3 single and multiple-choice answer options, respectively, on patient demographics (country of residence, gender, age), natural history, clinical signs and symptoms, triggers, associated diseases, and response to treatment. The diagnostic delay was defined as the period between the appearance of initial signs and symptoms of UV or CSU and time of diagnosis. The disease duration was defined as the period between the initial onset of signs and symptoms and the time patients were surveyed.

In addition, we generated wheal heat maps as previously described.(27, 28) Briefly, patients marked, on a silhouette of the human body, the typical areas affected by their wheals, which was then digitalized to show the pooled wheal distribution patterns in both patient groups. The study was conducted from January 2017 until December 2020.

Patient and Public Involvement

Patients and the public were involved in the dissemination plans of our research. During annual UCARE and Global Urticaria Forum Meetings (GUF) as well as the

UCARE website the public was informed about the plans of the research. Patient organizations were also informed about the project and a possible participation. Patients with urticarial vasculitis in a group on social media were informed about the study and will disseminate its results.

Statistical analysis

For all analyses, SPSS version 27.0 (Armonk, NY: IBM Corp, USA) and Microsoft Excel for Microsoft 365 MSO (Microsoft Corp, USA), R (Version 4.1.2.; R Foundation for Statistical Computing; package 'ggraph',' igraph',' tidyverse', 'ggpubr') and Python (version 3.7; Python Software Foundation; package 'matplotlib-venn') were used. Quantitative parameters were assessed as mean, standard deviation (SD), median, interquartile range, minimum and maximum values. To test for statistically significant differences between UV and CSU, but also between NUV, HUV, and CSU patients, the Chi-square test was used for bivariate and multivariate analysis of binary variables. If the expected cell count fell below 5, Fisher's exact test was used instead. For multivariate non-parametric analysis between NUV, HUV and CSU patients, the Kruskal-Wallis test was used. Other comparisons between groups were performed by Mann–Whitney U test for independent non-parametric variables and unpaired T-test for normally distributed data. Effect sizes were calculated using Cramers V for the Chi-square test and the Pearson correlation coefficient for the Mann-Whitney U test. Correlation analyses were performed by using Spearman's correlation coefficient. A p-value of ≤ 0.05 was considered to indicate statistical significance.

For multivariable analysis, a forward selection (likelihood ratio) logistic regression was conducted, taking the UV versus CSU diagnosis as a dependent variable, and the

following variables deemed of clinical importance as independent variables: wheal duration, clinical symptoms (pruritus, burning of the skin, pain of the skin, post-inflammatory hyperpigmentation, fever, abdominal complaints, muscle and bone pain, joint swelling and pain, eye inflammation, treatment efficacy of antihistamines, oral corticosteroids and omalizumab). In the final model, adjusted Odds Ratios were reported. Furthermore, a multiple linear regression was conducted, using the diagnosis delay as a dependent variable; first symptoms' manifestation and wheal duration of more than 24 hours were included in the model. After checking the assumptions of the model adequacy (residues normality, linearity, and homoscedasticity through appropriate plots and the absence of collinearity through variance inflation factor calculation), adjusted betas (B) were used to assess the association magnitude and direction between independent and diagnostic delay, in addition to their 95% CI.

Results

Patients with urticarial vasculitis and chronic spontaneous urticaria share demographic and clinical features

Patients with UV and patients with CSU were both predominantly middle-aged (mean age in years: UV 49.5 ± 16.8, CSU 46.0 ± 14.6), female (UV 82.1%, CSU 77.2%) and had a median body mass index of 24.7 (UV) and 25.0 (CSU) (**Table 1**).

More than 60% of UV and CSU patients reported stress as the most common trigger factor (**Table E2**).

All UV and CSU patients had wheals, and 66% and 62% had angioedema, respectively. As for initial signs and symptoms that occurred at disease onset, wheals (UV 95.3%, n=101; CSU 96.0%, n=121) and itch (UV 72.6%, n=77; CSU 88.9%, n=112, p<0.01) were the most frequently reported in both patient groups (**Table E2**, **Figure 1**). UV and CSU patients also reported a similar distribution pattern of wheals, with upper and lower extremities and the back being the most frequently affected parts of the body. As assessed by body heat maps, the cheeks, back of the hands, lower legs and the back were more often affected in CSU patients compared to UV patients (**Table E2**, **Figure E3**). Eyes (19.5% vs 0.0%, p=0.025) and thighs (71.3% vs 47.4%, p=0.045) were more often affected in female UV patients than in male UV patients. Comparison of biopsy-confirmed CSU and non-biopsy-confirmed CSU patients with UV patients in regard to demographic and clinical parameters were similar in both groups (**Table E3**).

Patients with UV show longer wheal duration and higher rates of burning, pain, post-inflammatory hyperpigmentation, and systemic signs and symptoms as compared to CSU patients

Most UV patients, but only one in five CSU patients, had wheals of ≥24 hours (63.1% vs. 20.8%; p<0.001), and 30.1% of UV patients, but only 8.8% of CSU patients had wheals of >48 hours duration (p<0.001, **Table E2, Figure 2**). In contrast, more CSU as compared to UV patients reported wheals of up to 12 hours duration (50.4% vs. 16.5%, p<0.001).

Post-inflammatory hyperpigmentation at sites of whealing occurred in 72.6% of UV patients and 20.6% of CSU patients (p<0.001). In UV vs CSU patients, post-inflammatory hyperpigmentation was more commonly associated with pruritus (67% vs 19.8%), skin pain (41.5% vs 9.5%), wheals ≥24 h duration (50% vs 7.9%), and systemic symptoms (54.7% vs 12.7%) (**Figure 3**).

Systemic signs and symptoms occurred in 72.6% (n=77) of UV patients as compared to 52.4% (n=66) of CSU patients. Common systemic signs and symptoms of UV patients included fatigue (54.7%), joint swelling/pain (42.5%), fever/chills (34.0%) and abdominal complaints (21.7%), and all of these were less common in patients with CSU (27.8%, 18.3%, 15.1%, 11.9%, respectively; all p<0.05). **(Table 1, Figure 1)**. UV patients more often had comorbid metabolic (25.5% vs 12.7%, p<0.01) and rheumatic (12.3% vs 4.8%, p<0.05) diseases than CSU patients.

Of all UV and CSU patients, 94.2% (n=97) and 64.8% (n=81), respectively, had wheals of ≥24h duration, post-inflammatory hyperpigmentation and/or any systemic signs and symptoms**.** Of them, 40.2% (n=39) of UV patients had all three clinical features as compared to only 7.4% (n=6) of CSU patients (**Figure 4**).

Compared to CSU patients, the risk for UV patients of experiencing post-inflammatory hyperpigmentation, wheals of ≥24h duration, eye inflammation and fever was 6.9, 4.0, 3.6 and 2.4 times greater, respectively. Inversely, pruritus was associated with a lower odds of UV versus CSU diagnosis (Odds ratio [ORa]=0.21) (**Figure 5)**.

In UV, normal complement levels, frequent whealing at disease onset, and abdominal symptoms are linked to delayed diagnosis

At disease onset, 54.7% of UV patients (n=58) experienced skin-related symptoms only, whereas 45.3% (n=48) also had systemic symptoms (**Table E2, Figure 1**). Burning, pain, and post-inflammatory hyperpigmentation of the skin were more common at disease onset and more often the first symptoms in UV patients as compared to CSU patients (**Table E2, Figure 1**).

Wheals of ≥24h duration (ORa=7.3), pain of the skin (ORa=7.0), post-inflammatory hyperpigmentation of the skin (ORa=4.1), and fatigue (ORa=3.1) as initial symptoms were significantly associated with UV diagnosis compared to CSU diagnosis; in contrast, having pruritus as first symptom was inversely associated with UV diagnosis (ORa=0.19).

UV patients, overall, experienced a numerically higher median (IQR) delay in diagnosis than CSU patients, i.e. 9 (4-44) and 6 (2-27) months, respectively (**Table 1**). Significant drivers of delayed UV diagnosis were normal complement levels, i.e. 21 (5-46) months vs 5 (3-12) months in HUV ($p<0.05$, **Table E4**), as well as a more frequent occurrence of wheals ($r=0.346$, $p<0.01$).

Among patients with UV, wheals of 24h duration or longer were significantly associated with a shorter delay in diagnosis (B=-40.97), whereas abdominal complaints (B=94.95)

as the first manifestation of the disease were significantly associated with increased diagnostic delay (**Table E5**).

Antihistamines, oral corticosteroids, and omalizumab are the most frequently used drugs in UV and CSU

The most frequently prescribed drugs for both UV and CSU were antihistamines (UV 93.4%; CSU 97.6%) and oral corticosteroids (UV 56.6%; CSU 50.0%), followed by omalizumab (UV 34.9%; CSU 38.9%) **(Figure 6, Table E2)**. UV patients more often received topical corticosteroids ($p<0.05$), pain killers ($p<0.001$), dapsone ($p<0.001$), (hydroxy)chloroquine ($p<0.001$), methotrexate ($p<0.01$), colchicine ($p<0.01$) and canakinumab ($p<0.05$) than CSU patients. (**Figure 6**, **Table E2**).

More UV than CSU patients who were treated with oral corticosteroids reported a strong improvement, 73.3% vs 50.8%% ($p<0.01$), and a lower number benefitted from omalizumab (40.5% vs 71.4%, $p<0.05$, **Table E6**).

Other commonly used treatments in UV included cyclosporine (18.9%), methotrexate (14.2%), dapsone (23.6%), and (hydroxy)chloroquine (29.2%), with responder rates (UV patients with significant improvement of symptoms) of 55.0%, 53.3%, 36.0%, and 29.0%, respectively. In CSU patients, response rates were highest (71.4%) for omalizumab, oral corticosteroids (50.8%) and cyclosporine (47.4%) (**Figure 6, Table E6-E8**).

Discussion

This is the first prospective international study that investigated differences and similarities between UV and CSU in terms of a wide range of demographic and clinical features including time to diagnosis, occurrence of skin and systemic symptoms, and need for anti-inflammatory treatment.

So far, only a few retrospective studies compared both diseases in smaller cohorts of UV patients for a limited number of parameters. One study from Turkey compared a cohort of n=146 CSU and n=43 UV patients in regard to demographics, natural history, concomitant diseases, laboratory results and treatments by review of patient files.(21) A study by Cherrez-Ojeda and co-workers focused on the comparison of UV (n=12) versus CSU patients (n=86) regarding thyroid autoimmunity.(29) Another study examined dermoscopy features in UV (n=27) versus CSU (n=108) patients.(30) Finally, we recently compared UV (n=46) to CSU patients (n=51) in regard to histological features.(20)

In the current study, we observed a similar age distribution and female predominance in both CSU and UV cohorts, which is in line with previous reports.(20) Disease duration is comparable for CSU and UV patients in our study (3.8 vs. 4.9 months), whereas another study reported longer disease duration for CSU patients (8.2 vs. 4.2 months), probably due to recruitment bias.(20)

All CSU and UV patients presented with wheals with or without angioedema. We did not observe convincing differences in wheal distribution between CSU and UV patients excluding this parameter as a reliable marker for distinguishing the two conditions. However, wheal duration was longer in UV patients, with wheals of ≥24h duration observed in the majority of UV patients and only in one-fifth of CSU patients (63% vs.

21%). Similarly, wheals lasting >24 hours have been reported in a smaller proportion of CSU patients (25.9%) as compared to UV patients (70.4%) before.(30) In line with one study(20) but not another(21), we could not confirm the more frequent occurrence of angioedema in CSU patients compared with UV patients. Pruritus was reported as a common initial symptom in UV patients in our study, however significantly less frequent than in CSU patients. High rates of pruritus in both UV and CSU groups have been reported in the past too.(20)

We showed higher rates of skin pain, burning of the skin, and post-inflammatory hyperpigmentation in UV patients as compared to CSU patients. In another study, skin pain and burning were assessed as one symptom in UV and CSU patients and no significant difference was observed.(30) However, the same study revealed a significantly higher rate of purpura/residual hyperpigmentation in UV (48.1%) compared to CSU (9.3%) patients.(30) Although some CSU patients also present with occasional bruising as described by us and others, histopathological findings do not significantly differ between CSU with or without bruising lesions as reported by Batista and colleagues.(31) In summary, we could show that the combination of wheal duration ≥24 hours, post-inflammatory hyperpigmentation and occurrence of systemic symptoms, especially eye inflammation and fever, is linked to UV diagnosis and can help to differentiate UV from CSU.

Systemic symptoms occur in 25.0% to 97.9% of UV patients(12, 15, 32, 33), which is in line with our study (72.6%). In our work and the literature(21), UV patients demonstrated higher rates of systemic symptoms compared to CSU patients. The prevalence of systemic symptoms in CSU patients, however, should be further investigated. A UCARE project “CSUplus” and the project “CUADSY” including data from the Chronic Urticaria Registry (CURE) will investigate whether those systemic

symptoms are true manifestations of CSU or appear due to other reasons, e.g. comorbidities.

UV patients had a longer diagnostic delay than CSU patients in this study (9 vs. 6 months) which was similar to our previous study (8.1 months for UV patients).(14) Patients with NUV demonstrated the longest diagnostic delay (21 months), which may be explained by the fact that NUV is clinically more similar to CSU than HUV. Gastrointestinal complaints are seen in 3 to 66% of UV patients(14, 17) and, as initial symptoms, were associated with delayed diagnosis in this study. This might be due to patients' initial visits to gastroenterologists, primary care physicians and other physicians before the link between gastrointestinal complaints and UV is established. Further studies should investigate how often gastrointestinal complains and other systemic symptoms are linked to UV itself, underlying diseases and/or comorbidities.

Antihistamines, oral corticosteroids, and omalizumab were the most frequently used drugs in UV and CSU patients. Compared to CSU, antihistamines are thought to be less effective in UV.(19) Also, corticosteroids are not a useful long-term therapeutic option in both diseases due to the side effect profile. Nonetheless, we observed that oral corticosteroids were more frequently effective in UV than in CSU. Omalizumab demonstrated, consistent with the literature,(19) a considerable improvement in 40.5% of UV patients, although at significantly lower rates than in CSU patients (71.4%).

Our manuscript has several strengths and limitations. This first international study involving multiple UCAREs allowed recruitment of a relevant number of patients with such a rare disease as UV. In all UV patients, diagnosis was confirmed by skin biopsy, the current gold standard for diagnosis.(7) However, not all CSU patients underwent skin biopsy due to a clear clinical picture, and complement levels were not available

for all UV patients. In addition, skin biopsies were not further examined in regard to recently published criteria. (20) Finally, ethnicity and laboratory findings such as C-reactive protein, erythrocyte sedimentation rate, IgE and autoantibodies were not assessed in our study.

Outlook

It is still unknown whether CSU and normocomplementemic UV represent distinct entities or if there is a disease continuum in a subpopulation of patients. For example, similarities between both conditions, e.g. systemic symptoms in some CSU patients and angioedema, itch, and good response to omalizumab in some UV patients, support the hypothesis that some patients can have both, CSU and UV, at different time points over the course of the disease. Furthermore, there are histologic features in individual patients that are attributed to UV in CSU patients and vice versa. (4, 20) It is also possible that the clinical and histological picture differs between CSU and UV patients depending on the disease activity. Additionally, there are further diagnostic marker and laboratory findings that could possibly help distinguishing the entities, which have not been surveyed in our study and should be addressed in future investigations. The Task Force of the European Academy of Allergy and Clinical Immunology consisting of an international panel of experts has developed a Delphi survey to examine whether CSU and NUV are different entities or part of a disease spectrum presenting with wheals; the results will be published soon. Prospective studies are also needed to further investigate this.

Conclusion

Taken together, our study provides evidence for a set of clinical criteria for the differentiation between UV and CSU. Long wheal duration (≥24h), skin pain and residual post-inflammatory hyperpigmentation, and systemic symptoms point to UV rather than CSU and should prompt further diagnostic work-up including a skin biopsy (proposed algorithm: **Figure 7**). A longer diagnostic delay for normocomplementemic UV indicates an unmet need for raising disease awareness among medical specialists to improve UV diagnosis and reduce the time from diagnosis to appropriate treatment of UV patients.

Acknowledgements:

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References

1. Kolkhir P, Giménez-Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. Nat Rev Dis Primers. 2022;8(1):61.
2. Dincy CV, George R, Jacob M, Mathai E, Pulimood S, Eapen EP. Clinicopathologic profile of normocomplementemic and hypocomplementemic urticarial vasculitis: a study from South India. Journal of the European Academy of Dermatology and Venereology : JEADV. 22. Netherlands2008. p. 789-94.
3. O'Donnell B, Black AK. Urticarial vasculitis. Int Angiol. 1995;14(2):166-74.
4. Cardoso PA, de Oliveira ZP, Alves VA, Candelori I, Croce J, Rivitti EA. Urticarial vasculitis. Allergol Immunopathol (Madr). 1990;18(4):191-5.
5. Peteiro C, Toribio J. Incidence of leukocytoclastic vasculitis in chronic idiopathic urticaria. Study of 100 cases. The American Journal of dermatopathology. 1989;11(6):528-33.
6. Tosoni C, Lodi-Rizzini F, Cinquini M, Pasolini G, Venturini M, Sinico RA, et al. A reassessment of diagnostic criteria and treatment of idiopathic urticarial vasculitis: a retrospective study of 47 patients. Clin Exp Dermatol. 34. England2009. p. 166-70.
7. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734-66.
8. E. Koç, B. Aksoy, and A. Tatlıparmak, 'Urticarial Vasculitis', A Comprehensive Review of Urticaria and Angioedema. InTech, May 31, 2017.
9. Carlson, J Andrew; Chen, Ko-Ron. Cutaneous Vasculitis Update: Small Vessel Neutrophilic Vasculitis Syndromes. The American Journal of Dermatopathology 28(6):p 486-506, December 2006.
10. Kolkhir P, Muñoz M, Asero R, Ferrer M, Kocatürk E, Metz M, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol. 2022;149(6):1819-31.

11. Arora A, Wetter DA, Gonzalez-Santiago TM, Davis MD, Lohse CM. Incidence of leukocytoclastic vasculitis, 1996 to 2010: a population-based study in Olmsted County, Minnesota. Mayo Clin Proc. 2014;89(11):1515-24.

12. Jachiet M, Flageul B, Deroux A, Le Quellec A, Maurier F, Cordoliani F, et al. The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients. Arthritis & rheumatology (Hoboken, NJ). 2015;67(2):527-34.

13. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. Immunol Allergy Clin North Am. 24. United States2004. p. 183-213, vi.

14. Bonnekoh H, Jelden-Thurm J, Butze M, Krause K, Maurer M, Kolkhir P. In urticarial vasculitis, long disease duration, high symptom burden and high need for therapy are linked to low patient-reported quality of life. J Allergy Clin Immunol Pract. 2022.

15. Mehregan DR, Gibson LE. Pathophysiology of urticarial vasculitis. Archives of dermatology. 1998;134(1):88-9.

16. Davis MD, Daoud MS, Kirby B, Gibson LE, Rogers RS, 3rd. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. J Am Acad Dermatol. 1998;38(6 Pt 1):899-905.

17. Kulthanan K, Cheepsomsong M, Jiamton S. Urticarial vasculitis: etiologies and clinical course. Asian Pac J Allergy Immunol. 2009;27(2-3):95-102.

18. Sjöwall C, Mandl T, Skattum L, Olsson M, Mohammad AJ. Epidemiology of hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis). Rheumatology (Oxford). 2018;57(8):1400-7.

19. Kolkhir P, Grakhova M, Bonnekoh H, Krause K, Maurer M. Treatment of urticarial vasculitis: A systematic review. The Journal of allergy and clinical immunology. 2019;143(2):458-66.

20. Puhl V, Bonnekoh H, Scheffel J, Hawro T, Weller K, von den Driesch P, et al. A novel histopathological scoring system to distinguish urticarial vasculitis from chronic spontaneous urticaria. Clin Transl Allergy. 2021;11(2):e12031.

21. Akarsu S, İlknur T, Özbağçıvan Ö, Fetil E. Accompanying conditions in patients with chronic spontaneous urticaria and urticarial vasculitis: results of a retrospective study.: Türkderm 2015. p. 18-24.

22. Doong JC, Chichester K, Oliver ET, Schwartz LB, Saini SS. Chronic Idiopathic Urticaria: Systemic Complaints and Their Relationship with Disease and Immune Measures. J Allergy Clin Immunol Pract. 2017;5(5):1314-8.

23. Sabroe RA, Poon E, Orchard GE, Lane D, Francis DM, Barr RM, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcepsilonRI or anti-IgE autoantibodies. J Allergy Clin Immunol. 103. United States1999. p. 484-93.

24. Sibbald RG, Cheema AS, Lozinski A, Tarlo S. Chronic urticaria. Evaluation of the role of physical, immunologic, and other contributory factors. Int J Dermatol. 1991;30(6):381-6.

25. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. Br J Dermatol. 1981;104(4):369-81.

26. Maurer M, Metz M, Bindslev-Jensen C, Bousquet J, Canonica GW, Church MK, et al. Definition, aims, and implementation of GA(2) LEN Urticaria Centers of Reference and Excellence. Allergy. 2016;71(8):1210-8.

27. Hawro T, Przybyłowicz K, Spindler M, Hawro M, Steć M, Altrichter S, et al. The characteristics and impact of pruritus in adult dermatology patients: A prospective, cross-sectional study. Journal of the American Academy of Dermatology. 2021;84(3):691-700.

28. Hawro M, Sahin E, Steć M, Różewicka-Czabańska M, Raducha E, Garanyan L, et al. A comprehensive, tri-national, cross-sectional analysis of characteristics and impact of pruritus in psoriasis. J Eur Acad Dermatol Venereol. 2022;36(11):2064-75.

654 29. Cherrez-Ojeda I, Vanegas E, Mata VL, Felix M, Ramon GD, Cherrez S, et al. Autoimmune
655 thyroid disease and urticarial vasculitis: is there a significant association? Allergy Asthma Clin
656 Immunol. 2019;15:25.
657 30. García-García B, Aubán-Pariente J, Munguía-Calzada P, Vivanco B, Argenziano G, Vázquez-
658 López F. Development of a clinical-dermoscopic model for the diagnosis of urticarial vasculitis. Sci
659 Rep. 2020;10(1):6092.
660 31. Batista M, Calado R, Gil F, Cardoso JC, Tellechea O, Gonçalo M. Histopathology of chronic
661 spontaneous urticaria with occasional bruising lesions is not significantly different from urticaria with
662 typical wheals. J Cutan Pathol. 2021;48(8):1020-6.
663 32. Callen JP, Kalbfleisch S. Urticarial vasculitis: a report of nine cases and review of the
664 literature. Br J Dermatol. 1982;107(1):87-93.
665 33. Sanchez NP, Winkelmann RK, Schroeter AL, Dicken CH. The clinical and histopathologic
666 spectrums of urticarial vasculitis: study of forty cases. J Am Acad Dermatol. 1982;7(5):599-605.

FIGURE LEGENDS:

Figure 1: Number of UV (black line) and CSU (white line) patients presenting with skin (A) and systemic (B) symptoms as first manifestation, at the moment of inclusion (currently) and ever occurred (over time). The exact data and p-values are displayed in Supplement Table 3. The solid lines represent course of time.

Figure 2: Duration of A) wheals and B) angioedema in patients with urticarial vasculitis (UV, black bars) and patients with chronic spontaneous urticaria (CSU, white bars).

Figure 3: Symptoms and treatment response. Interrelations between the clinical manifestations in patients with UV (left) and CSU (right). Bubble diameter is proportional to the proportion of individuals with the symptom category reported. Line thickness is proportional to the number of individuals with the coexisting manifestations, i.e. the joint occurrence of two symptoms. PI, postinflammatory; oral corticosteroids, OMA and AH present significant treatment effect with oral corticosteroids, omalizumab and antihistamines, respectively.

Figure 4: As compared to CSU patients, UV patients show higher rates of all three clinical features, i.e. wheals of ≥24h duration, post-inflammatory hyperpigmentation and any systemic signs and symptoms. All UV (left) and CSU (right) patients who had wheals of ≥24h duration (UV: n=65/106, CSU: n=26/126), post-inflammatory hyperpigmentation (UV: n=77/106, CSU: n=26/126) and/or any systemic symptoms (UV: n=77/106, CSU: n=66/126) ever occurred.

692 **Figure 5:** Higher risk for patients with urticarial vasculitis of experiencing post-
693 inflammatory hyperpigmentation, wheals of ≥24h duration, eye inflammation and fever
694 compared to patients with chronic spontaneous urticaria. Results of binomial
695 regression.

696

697 **Figure 6:** Frequency and efficacy of treatments in patients with urticarial vasculitis
698 (UV) and patients with chronic spontaneous urticaria (CSU). Several responses from
699 the same patient were allowed.

700

701 **Figure 7:** Algorithm for differential diagnosis between urticarial vasculitis and chronic
702 spontaneous urticaria in patients initially presenting with wheals.

703 *Cave: Systemic symptoms may also point towards autoinflammatory diseases.

TABLES:

Table 1. Characteristics of patients with urticarial vasculitis (UV) and chronic spontaneous urticaria (CSU).

Parameter		Total population (n=232)	Urticarial vasculitis (n=106)*	Chronic spontaneous urticaria (n=126)*	P-Value	Effect size
Gender, % (n of 229)	**Female**	79.5 (182)	82.1 (87)	77.2 (95)	0.366	–
	Male	20.5 (47)	17.9 (19)	22.8 (28)		
Age, years (total n=214), mean (range), SD		47.6 (17.0-88.0), 15.7	49.5 (21.0-88.0), 16.8	46.0 (17.0-80.0), 14.6	0.109	–
Age at onset, years (total n=163), mean (range), SD		37.5 (0.0-76.0), 15.5	39.3 (3.0-76.0), 15.9	35.9 (0.0-76.0), 15.1	0.169	–
Diagnostic delay, months (total n=160), median (IQR)		8.0 (3.0-36.8)	9.0 (4.0-44.0)	6.0 (2.0-27.0)	0.158	–
Disease duration, months (total n=175), median (IQR)		50.2 (20.1-106.9)	59.5 (23.1-117.0)	45.9 (19.0-95.7)	0.419	–
Body mass index (total n=226), median (IQR)		24.9 (21.9-28.6)	24.7 (22.1-28.4)	25.0 (21.8-29.1)	0.950	–
Concomitant diseases, % (n of 232)	**Cardiovascular**	24.1 (56)	27.4 (29)	21.4 (27)	0.174	–
	Metabolic	18.5 (43)	25.5 (27)	12.7 (16)	**0.008**	0.174
	Autoimmune	14.7 (34)	12.3 (13)	16.7 (21)	0.433	–
	Rheumatic	8.6 (20)	12.3 (13)	4.8 (6)	**0.038**	0.136
	Lung related	6.5 (15)	7.5 (8)	5.6 (7)	0.539	–
	Kidney related	6.0 (14)	4.7 (5)	7.1 (9)	0.440	–
	Mental	6.0 (14)	3.8 (4)	7.9 (10)	0.185	–
	Gastroenterological	4.3 (10)	4.7 (5)	4.0 (5)	0.781	–
	Cancer	3.9 (9)	5.7 (6)	2.4 (3)	0.894	–
	Liver related	3.4 (8)	0.9 (1)	5.6 (7)	0.074	–
	Neurological	2.6 (6)	0.0 (0)	4.8 (6)	**0.008**	0.149
Clinical symptoms ever experienced, % (n of 232)	**Wheals, rash**	100.0 (232)	100.0 (106)	100.0 (126)	1.000	
	Itching	93.5 (217)	89.6 (95)	96.8 (122)	**0.026**	0.146
	Angioedema	63.8 (148)	66.0 (70)	61.9 (78)	0.514	–
	Burning of the skin	59.1 (137)	65.1 (69)	54.0 (68)	0.086	–
	Post-inflammatory hyperpigmentation	44.4 (103)	72.6 (77)	20.6 (26)	**<0.001**	0.521
	Lethargy, fatigue	40.1 (93)	54.7 (58)	27.8 (35)	**<0.001**	0.274
	Pain of the skin	31.9 (74)	49.1 (52)	17.5 (22)	**<0.001**	0.338
	Joint swelling/ pain	29.3 (68)	42.5 (45)	18.3 (23)	**<0.001**	0.265
	Fever, chills	23.7 (55)	34.0 (36)	15.1 (19)	**0.001**	0.221
	Muscle/ bone aches	21.1 (49)	31.1 (33)	12.7 (16)	**0.001**	0.225
	Eye redness/ inflammation	16.8 (39)	28.3 (30)	7.1 (9)	**<0.001**	0.282
	Abdominal complaints	16.4 (38)	21.7 (23)	11.9 (15)	**0.045**	0.132
	Swelling of lymph node	8.2 (19)	16.0 (17)	1.6 (2)	**<0.001**	0.263
	Ever occured systemic symptoms	61.6 (143)	72.6 (77)	52.4 (66)	**0.002**	0.208

IQR: interquartile range; QoL: Quality of life; SD: standard deviation. Tests used: Chi-square test for analysis of binary variables (If the expected cell count fell below 5, Fisher's exact test was used instead). Mann–Whitney U test for independent non-parametric variables. Unpaired T-test for normally distributed data. Effect sizes were calculated using Cramers V for the Chi-square test and the Pearson correlation coefficient for the Mann-Whitney U test.

Figure No. 1

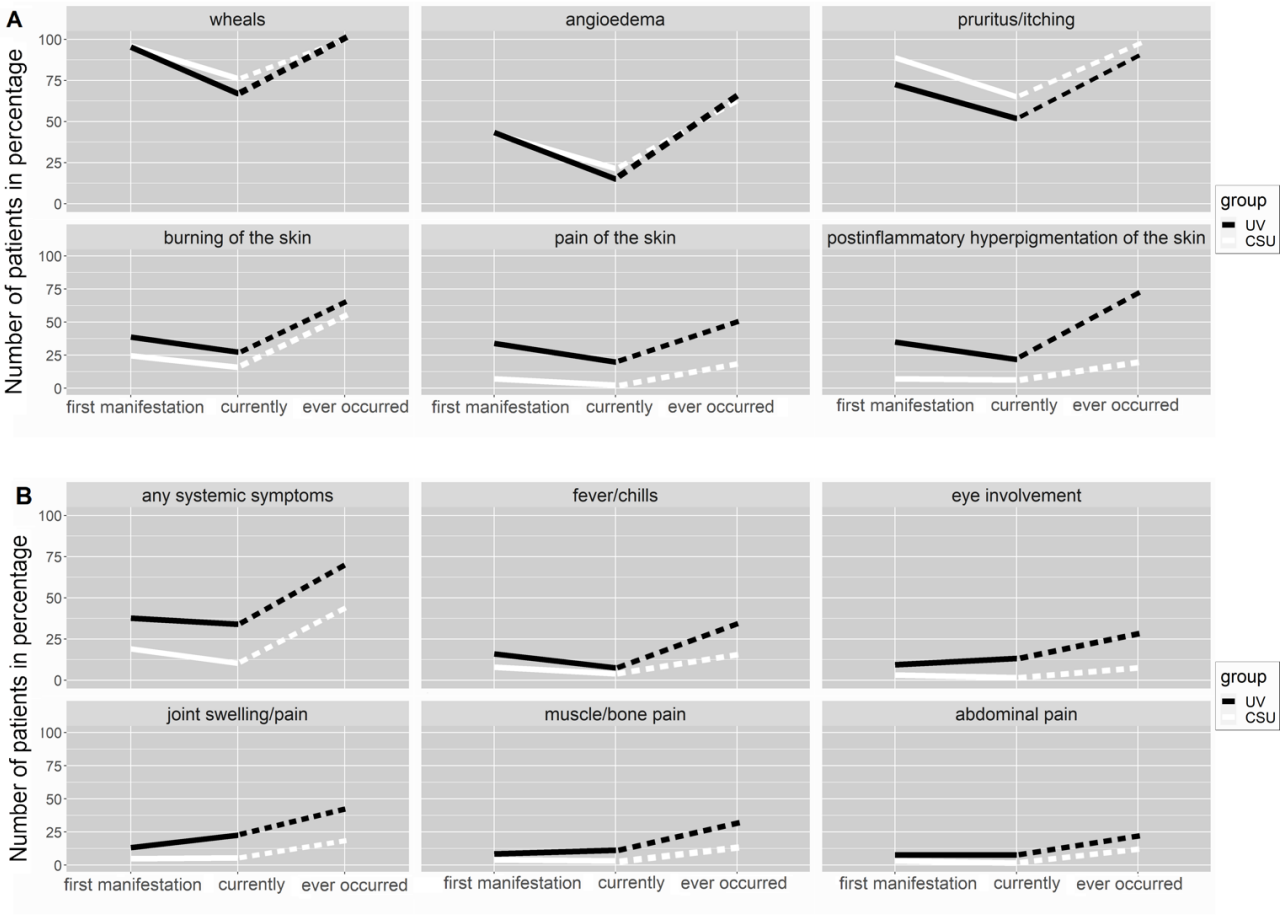


Figure 1_Bonnekoh et al.

Figure No. 2

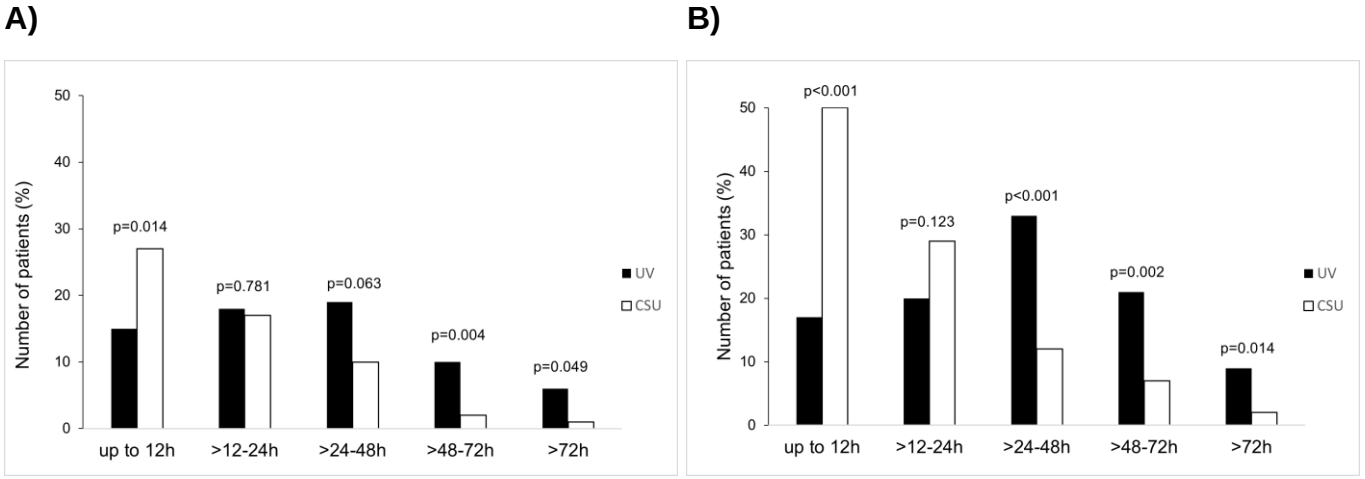
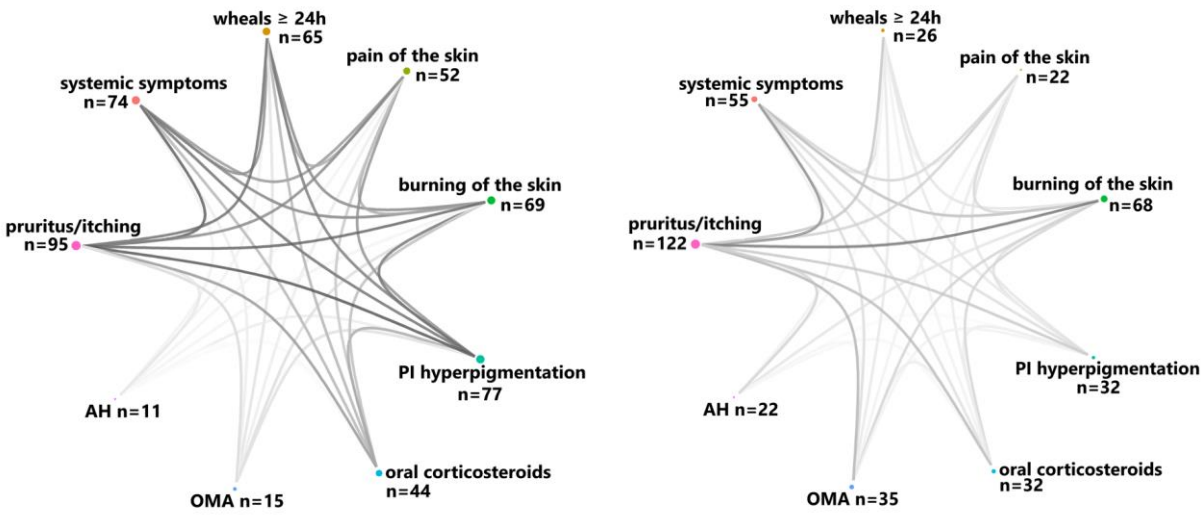


Figure 2_Bonnekoh et al.

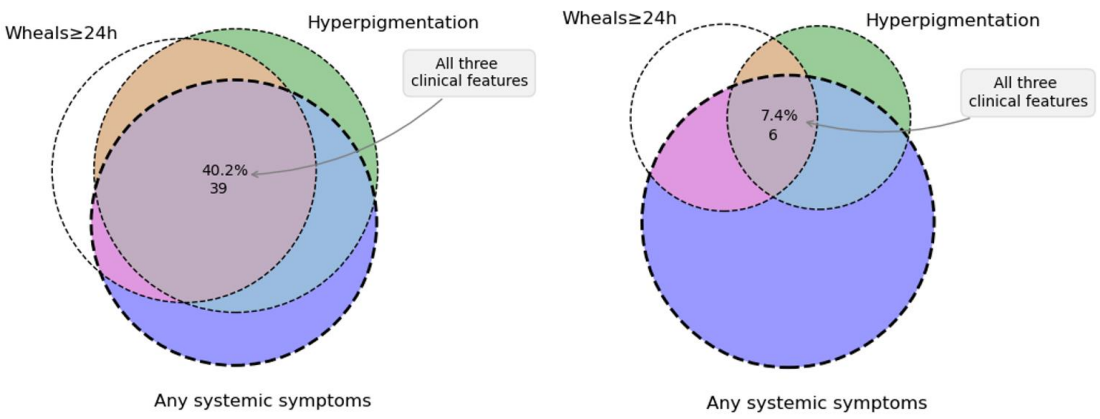
Figure No. 3



Urticarial vasculitis (UV) **Chronic spontaneous urticaria (CSU)**

Figure 3_Bonnekoh et al.

Figure No. 4



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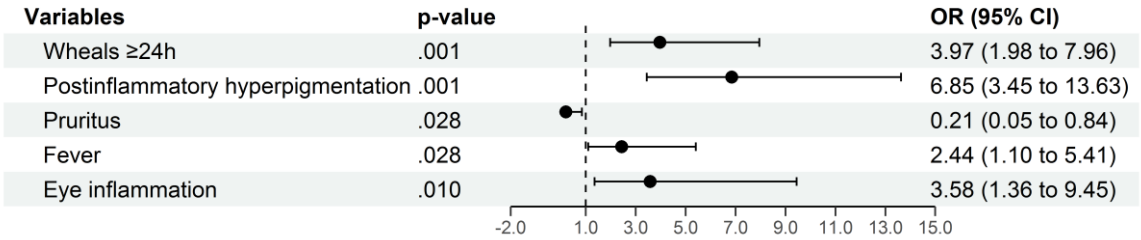

Figure 5_Bonnekoh et al.

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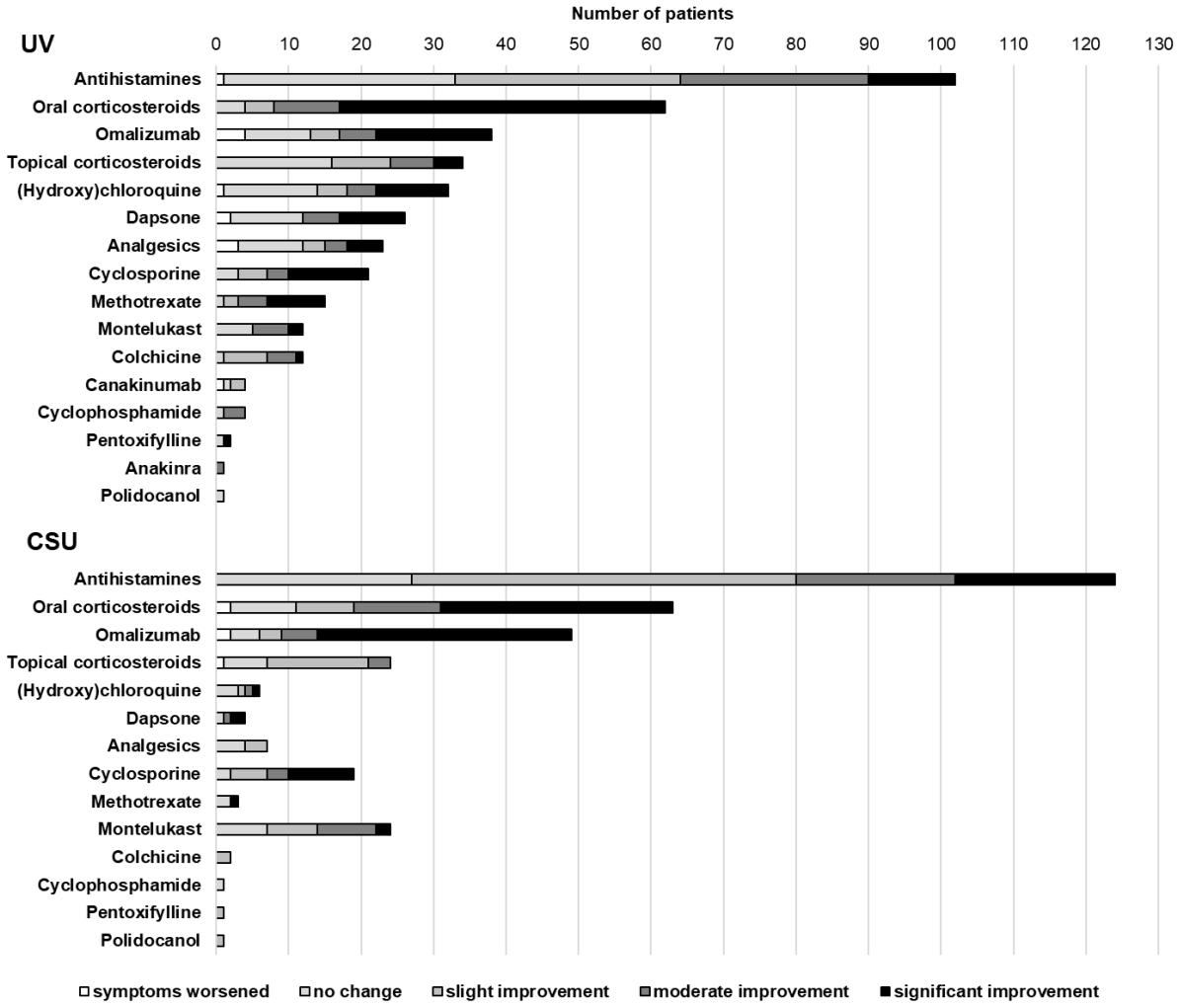

Figure 6_Bonnekoh et al.

Figure No. 7

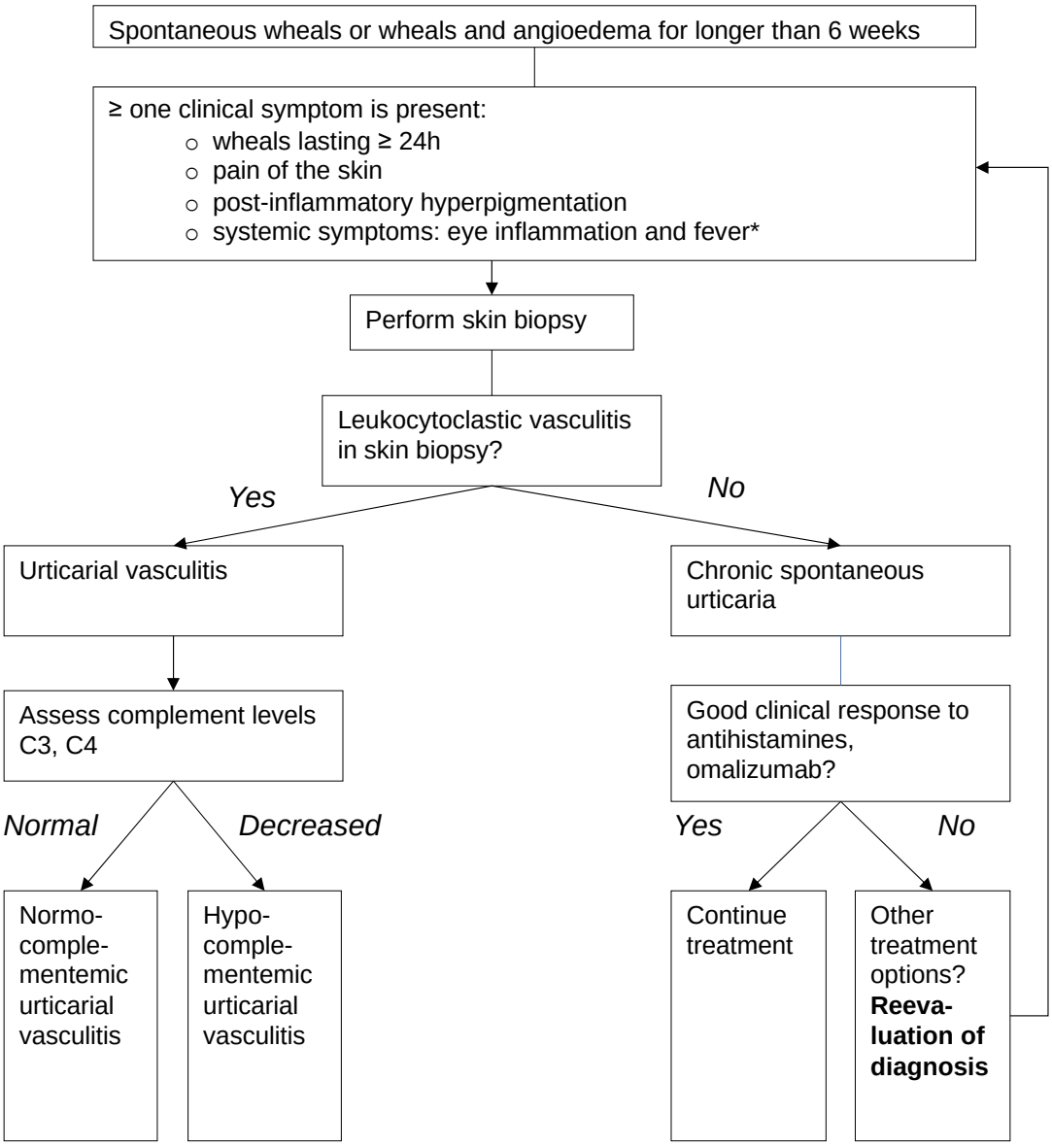

Figure 7_Bonnekoh et al.

Online Repository

ONLINE REPOSITORY FIGURE LEGENDS:

Figure E1: Exemplified histological images of the lesional skin of a patient with A) chronic spontaneous urticaria and B) urticarial vasculitis. Original magnification 100x

Figure E2: Questionnaire

Figure E3: A) Anatomical distribution of skin lesions in patients with urticarial vasculitis (UV, black) and chronic spontaneous urticaria (CSU, white) assessed by the questionnaire and B) demonstrated using body heat maps UV (left, n=75) and CSU (right, n=100). The colors code frequencies of reported skin lesions. Frequency range and color coding different frequencies within this range are presented on color bars. White relates to maximal (61%) and black refers to the minimal frequency (8%) of reported skin lesions of the total 239 534 pixels pro whole body. Front followed by the back side. Localization of angioedema was not recorded.

ONLINE REPOSITORY TABLE LEGENDS:

Table E1: Distribution and characteristics of patients with urticarial vasculitis (UV) and chronic spontaneous urticaria (CSU) by nationality

Table E2: Frequency and duration of wheals, diurnal occurrence, trigger factors and treatment use in patients with urticarial vasculitis and chronic spontaneous urticaria.

Table E3: Results of comparisons in terms of different demographic and clinical parameters were similar for group 1 (comparisons between UV patients and patients with biopsy-confirmed

CSU) and group 2 (comparisons between UV patients and patients with CSU without biopsy), apart from disease duration which was significantly longer in CSU patients from the first group and no difference was shown in the second group.

Table E4: Characteristics of patients with normocomplementemic urticarial vasculitis (NUV), hypocomplementemic vasculitis (HUV) and chronic spontaneous urticaria (CSU). IQR: interquartile range; QoL: Quality of life; SD: standard deviation. *Complement levels were available for 74 UV patients.

Table E5: Correlates of diagnostic delay in UV patients. Multiple regression model.

Table E6: Comparison of treatment efficacy between groups

Table E7: Treatment effects in patients with urticarial vasculitis.

Table E8: Treatment effects in patients with chronic spontaneous urticaria.

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TABLES

Table E1:

Nationality, % (n of 232)	Russia	Germany	Turkey	Brazil	China	Oman	Iran	Ecuador
Total population (n=232)	25.0 (58)	24.1 (56)	18.1 (42)	11.2 (26)	8.6 (20)	6.0 (14)	5.6 (13)	1.3 (3)
UV (n=106)*	23.6 (25)	29.2 (31)	15.1 (16)	12.3 (13)	9.4 (10)	3.8 (4)	3.8 (4)	2.8 (3)
CSU (n=126)*	26.2 (33)	19.8 (25)	20.6 (26)	10.3 (13)	7.9 (10)	7.9 (10)	7.1 (9)	0 (0)
Median diagnostic delay UV, months	9.0 (21)	12.0 (20)	6.0 (8)	10.0 (12)	7.0 (10)	15.0 (3)	39.0 (3)	3.0 (2)
Median diagnostic delay CSU, months	4.0 (23)	32.0 (20)	4.0 (8)	17.5 (8)	5.0 (9)	4.0 (5)	2.0 (8)	0.0 (0)
Antihistamine use in UV	100.0 (25)	90.3 (28)	93.8 (15)	100.0 (13)	90.0 (9)	100.0 (4)	50.0 (2)	100.0 (3)
Antihistamine use in CSU	97.0 (32)	100.0 (25)	96.2 (25)	100.0 (13)	100.0 (10)	90.0 (9)	100.0 (9)	0.0 (0)
Omalizumab use in UV	20.0 (5)	38.7 (12)	56.3 (9)	30.8 (4)	70.0 (7)	0.0 (0)	0.0 (0)	0.0 (0)
Omalizumab use in CSU	33.3 (11)	36.0 (9)	46.2 (12)	38.5 (5)	40.0 (4)	80.0 (8)	0.0 (0)	0.0 (0)
Oral corticosteroid use in UV	72.0 (18)	61.3 (19)	75.0 (12)	38.5 (5)	30.0 (3)	25.0 (1)	50.0 (2)	0.0 (0)
Oral corticosteroid use in CSU	42.4 (14)	84.0 (21)	57.7 (15)	46.2 (6)	40.0 (4)	20.0 (2)	11.1 (1)	0.0 (0)

Table E2:

Parameter		Total population (n=232)	Urticarial vasculitis (n=106)*	Chronic spontaneous urticaria (n=126)*	P-Value	Effect size
Frequency of wheals, % (n of 214)	**daily**	20.6 (44)	19.1 (18)	21.7 (26)	0.479	–
	nearly every day	13.6 (29)	16.0 (15)	11.7 (14)	0.486	–
	several times a week	20.1 (43)	19.1 (18)	20.8 (25)	0.577	–
	several times a month	10.7 (23)	9.6 (9)	11.7 (14)	0.506	–
	irregular intervals	35.0 (75)	36.2 (34)	34.2 (41)	0.940	–
Wheal duration, % (n of 228)	**up to 12 hours**	35.1 (80)	16.5 (17)	50.4 (63)	**<0.001**	0.353
	> 12 hours	64.9 (148)	83.5 (86)	49.6 (62)		
	up to 24 hours	60.1 (137)	36.9 (38)	79.2 (99)	**<0.001**	0.430
	> 24 hours	39.9 (91)	63.1 (65)	20.8 (26)		
	up to 48 hours	81.6 (186)	69.9 (72)	91.2 (114)	**<0.001**	0.273
	> 48 hours	18.4 (42)	30.1 (31)	8.8 (11)		
Time of the day, % (n of 227)*	**in the morning**	18.5 (42)	23.6 (25)	13.5 (17)	**0.047**	0.131
	at noon	2.6 (6)	1.9 (2)	3.2 (4)	0.691	–
	in the evening	20.7 (47)	23.6 (25)	17.5 (22)	0.248	–
	at night	22.5 (51)	27.4 (29)	17.5 (22)	**0.070**	0.119
	no specific time	56.4 (128)	52.8 (56)	57.1 (72)	0.511	–
Trigger, % (n of 151)*	**stress**	68.2 (103)	68.6 (48)	67.9 (55)	0.803	–
	infection	29.8 (45)	32.9 (23)	27.2 (22)	0.416	–
	other	29.8 (45)	28.6 (20)	30.9 (25)	0.852	–
	warmth/sweating	19.9 (30)	20.0 (14)	19.8 (16)	0.908	–
	physical exertion	15.9 (24)	17.1 (12)	14.8 (12)	0.654	–
	new medication	15.2 (23)	18.6 (13)	12.3 (10)	0.272	–
	cold	14.6 (22)	18.6 (13)	11.1 (9)	0.185	–
	UV rays	9.3 (14)	10.0 (7)	8.6 (7)	0.738	–
Performance restrictions at work, percent (total n=112), median (IQR)		40.0 (20.0-63.8)	40.0 (20.0-60.0)	35.0 (20.0-68.8)	0.793	–
Body parts affected by wheals, % (n of 232)	**Upper legs**	62.1 (144)	67.0 (71)	57.9 (73)	0.157	
	Arms	56.9 (132)	59.4 (63)	54.8 (69)	0.474	
	Lower legs	48.3 (112)	51.9 (55)	45.2 (57)	0.313	
	Back	47.8 (111)	44.3 (47)	50.8 (64)	0.327	
	Hands	42.2 (98)	40.6 (43)	43.7 (55)	0.636	
	Breast	37.5 (87)	42.5 (45)	33.3 (42)	0.153	
	Face	35.3 (82)	33.0 (35)	37.3 (47)	0.497	
	Neck	31.0 (72)	29.2 (31)	32.5 (41)	0.589	
	Varying locations	31.0 (72)	27.4 (29)	34.1 (43)	0.267	
	Feet	26.3 (61)	31.1 (33)	22.2 (28)	0.125	
	Abdominal	24.1 (56)	27.4 (29)	21.4 (27)	0.293	
	Lips	19.0 (44)	17.9 (19)	19.8 (25)	0.711	
	Eyes	17.7 (41)	16.0 (17)	19.0 (24)	0.549	
	Scalp	16.8 (39)	22.6 (24)	11.9 (15)	**0.029**	0.143
	Cheeks	12.5 (29)	15.1 (16)	10.3 (13)	0.273	
Clinical symptoms at onset of disease, % (n of 232)	**Wheals, rash**	95.7 (222)	95.3 (101)	96.0 (121)	0.780	
	Itching	81.5 (189)	72.6 (77)	88.9 (112)	**0.002**	0.208
	Angioedema	43.1 (100)	43.4 (46)	42.9 (54)	0.934	
	Burning of the skin	31.0 (72)	38.7 (41)	24.6 (31)	**0.021**	0.152

	Post-inflammatory hyperpigmentation	19.8 (46)	34.9 (37)	7.1 (9)	**<0.001**	0.347
	Pain of the skin	19.4 (45)	34.0 (36)	7.1 (9)	**<0.001**	0.338
	Lethargy, fatigue	17.2 (40)	27.4 (29)	8.7 (11)	**<0.001**	0.246
	Fever, chills	11.6 (27)	16.0 (17)	7.9 (10)	0.055	
	Joint swelling/ pain	8.6 (20)	13.2 (14)	4.8 (6)	**0.022**	0.150
	Muscle/ bone aches	6.0 (14)	8.5 (9)	4.0 (5)	0.150	
	Eye redness/ inflammation	6.0 (14)	9.4 (10)	3.2 (4)	**0.046**	0.131
	Abdominal complaints	5.2 (12)	7.5 (8)	3.2 (4)	0.134	
	Swelling of lymph node	2.2 (5)	3.8 (4)	0.8 (1)	0.181	
Treatment (Frequency of use), % (n of 232	**Antihistamines**	95.7 (222)	93.4 (99)	97.6 (123)	0.192	–
	Oral corticosteroids	53.0 (123)	56.6 (60)	50.0 (63)	0.315	–
	Omalizumab	37.1 (86)	34.9 (37)	38.9 (49)	0.531	–
	Topical corticosteroids	25.9 (60)	32.1 (34)	20.6 (26)	**0.047**	0.130
	Cyclosporine	16.8 (39)	18.9 (20)	15.1 (19)	0.442	–
	(Hydroxy)chloroquine	15.9 (37)	29.2 (31)	4.8 (6)	**<0.001**	0.333
	Montelukast	15.5 (36)	11.3 (12)	19.0 (24)	0.105	–
	Dapsone	12.5 (29)	23.6 (25)	3.2 (4)	**<0.001**	0.307
	Analgesics	12.5 (29)	20.8 (22)	5.6 (7)	**<0.001**	0.229
	Methotrexate	7.8 (18)	14.2 (15)	2.4 (3)	**0.001**	0.219
	Colchicine	6.0 (14)	11.3 (12)	1.6 (2)	**0.002**	0.204
	Cyclophosphamide	2.2 (5)	3.8 (4)	0.8 (1)	0.181	–
	Canakinumab	1.7 (4)	3.8 (4)	0.0 (0)	**0.042**	0.144
	Pentoxifylline	1.3 (3)	1.9 (2)	0.8 (1)	0.594	–
	Polidocanol	0.9 (2)	0.9 (1)	0.8 (1)	1.000	–
	Anakinra	0.4 (1)	0.9 (1)	0.0 (0)	0.457	–

*several answers were allowed

Table E3:

Parameter		UV (n=106)	CSU biopsy-confirmed (n=31)	P-value group 1	CSU non-biopsy-confirmed (n=83)	P-value group 2
Age, years (mean)		49.5	46.3	0.358	44.3	0.083
Age at onset, years (mean)		39.3	39.9	0.868	33.3	0.064
Sex, % (n)	**male**	19 (18)	26 (8)	0.332	23 (19)	0.329
	female	87 (82)	74 (23)		73 (61)	
Diagnostic delay, months (median, IQR)		9.0 (4-44)	4.5 (2-37)	0.132	6.5 (3-27)	0.421
Disease duration, months (median, IQR)		59.5 (23-117)	31.9 (12-65)	**0.033**	61.3 (26-108)	0.772
Body mass index, median (IQR)		24.7 (22-28)	24.8 (21-27)	0.350	24.9 (22-30)	0.469
Frequency of wheals, % (n)	**daily**	17.0 (18)	12.9 (4)	0.782	19.3 (34)	0.683
	nearly every day	14.2 (15)	12.9 (4)	0.860	12.0 (10)	0.672
	several times a week	17.0 (18)	19.4 (6)	0.760	21.7 (18)	0.414
	several times a month	8.5 (9)	16.1 (5)	0.308	9.6 (8)	0.784
	irregular intervals	32.1 (34)	25.8 (8)	0.505	34.9 (29)	0.678
Wheal duration, % (n)	**up to 12 hours**	16.5 (17)	51.6 (16)	**<0.001**	50.0 (41)	**<0.001**
	> 12 hours	83.5 (86)	48.4 (15)		50.0 (41)	
	up to 24 hours	36.9 (38)	77.4 (24)	**<0.001**	79.3 (65)	**<0.001**
	> 24 hours	63.1 (65)	22.6 (7)		20.7 (17)	
	up to 48 hours	69.9 (72)	90.3 (28)	**0.022**	92.7 (76)	**<0.001**
	> 48 hours	30.1 (31)	9.7 (3)		7.3 (6)	
Performance restrictions at work, percent, median (IQR)		40.0 (20-60)	30.0 (20-50)	0.587	50.0 (20-70)	0.327

Table E4:

Parameter		CSU (1) (n=126)	NUV (2) (n=58)*	HUV (3) (n=16)*	P-Value	Pairwise comparison	Effect size
Gender, % (n of 229)	**Female**	77.2 (95)	86.2 (50)	81.3 (13)	0.393	1 vs 2 vs 3	–
	Male	22.8 (28)	13.8 (8)	18.8 (3)			
Age, years (total n=214), mean (range), SD		46.0 (17.0-80.0), 14.6	49.4 (22.0-87.0), 17.5	49.9 (21.0-78.0), 15.2	0.494	Kruskal-Wallis	–
Age at onset, years (total n=163), mean (range), SD		35.9 (0.0-76.0), 15.1	40.1 (11.0-76.0), 16.7	37.8 (17.0-57.0), 12.9	0.522	Kruskal-Wallis	–
Diagnostic delay, months (total n=160), median (IQR)		6.0 (2.0-27.0)	21.0 (5.0-45.8)	5.0 (2.5-11.5)	**0.034** **0.019** **0.048**	Kruskal-Wallis 1 vs 2 2 vs 3	0.217 0.208 0.257
Disease duration, months (total n=175), median (IQR)		45.9 (19.0-95.7)	51.0 (17.2-108.0)	47.6 (26.3-110.3)	0.975	Kruskal-Wallis	–
Body mass index (total n=226), median (IQR)		25.0 (21.8-29.1)	25.0 (22.0-28.0)	22.6 (2.2-25.7)	0.324	Kruskal-Wallis	–
Performance restriction at work, % (total n=112), median (IQR)		35.0 (20.0-68.8)	30.0 (11.3-50.0)	30.0 (10.0-50.0)	0.301	Kruskal-Wallis	–
Incapacity for work, days (total n=64), median (IQR)		30.0 (14.0-50.0)	37.5 (13.5-50.0)	90.8 (7.0-205.0)	0.912	Kruskal-Wallis	–
Wheal duration, % (n of 196)	**Up to 12 hours**	50.4 (63)	10.9 (6)	25.0 (4)	**<0.001**	1 vs 2 vs 3	0.368
	> 12 hours	49.6 (62)	89.1 (49)	75.0 (12)	**<0.001**	1 vs 2	0.374
	Up to 24 hours	79.2 (99)	30.9 (17)	56.3 (9)	**<0.001** **<0.001**	1 vs 2 vs 3 1 vs 2	0.446 0.465
	> 24 hours	20.8 (26)	69.1 (38)	43.8 (7)			
	Up to 48 hours	91.2 (114)	74.5 (41)	68.8 (11)	**0.002** **0.003** **0.020**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.243 0.222 0.225
	> 48 hours	8.8 (11)	25.5 (14)	31.3 (5)			
Concomitant diseases, % (n of 232)	**Cardiovascular**	21.4 (27)	29.3 (17)	12.5 (2)	0.316	1 vs 2 vs 3	–
	Metabolic	12.7 (16)	31.0 (18)	25.0 (4)	**0.010** **0.003**	1 vs 2 vs 3 1 vs 2	0.213 0.219
	Other diseases	24.6 (31)	10.3 (6)	0.0 (0)	**<0.001** **<0.001** **0.004**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.312 0.263 0.243
	Autoimmune	16.7 (21)	12.1 (7)	6.3 (1)	0.585	1 vs 2 vs 3	–
	Rheumatic	5.6 (7)	15.5 (9)	0.0 (0)	**0.030** **0.013**	1 vs 2 vs 3 1 vs 2	0.200 0.183
	Lung related	5.6 (7)	8.6 (5)	12.5 (2)	0.319	1 vs 2 vs 3	–
	Kidney related	7.1 (9)	6.9 (4)	6.3 (1)	1.000	1 vs 2 vs 3	–
	Mental	7.9 (10)	5.2 (3)	6.3 (1)	0.905	1 vs 2 vs 3	–
	Gastroenterological	4.0 (5)	5.2 (3)	0.0 (0)	1.000	1 vs 2 vs 3	–
	Cancer	2.4 (3)	5.2 (3)	6.3 (1)	0.348	1 vs 2 vs 3	–
	Liver related	5.6 (7)	1.7 (1)	0.0 (0)	0.509	1 vs 2 vs 3	–
	Neurological	4.8 (6)	0.0 (0)	0.0 (0)	0.288	1 vs 2 vs 3	–
Treatment (Frequency of use), % (n of 232)	**Antihistamines**	97.6 (123)	93.1 (54)	93.8 (15)	0.260	1 vs 2 vs 3	–
	Oral corticosteroids	50.0 (63)	50.0 (29)	62.5 (10)	0.644	1 vs 2 vs 3	–
	Omalizumab	38.9 (49)	39.7 (23)	56.3 (9)	0.424	1 vs 2 vs 3	–

	Topical corticosteroids	20.6 (26)	29.3 (17)	25.0 (4)	0.434	1 vs 2 vs 3	–
	Cyclosporine	15.1 (19)	15.5 (9)	43.8 (7)	**0.029** **0.011** **0.034**	1 vs 2 vs 3 1 vs 3 2 vs 3	0.204 0.234 0.282
	(Hydroxy)chloroquine	4.8 (6)	27.6 (16)	43.8 (7)	**<0.001** **<0.001** **<0.001**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.379 0.327 0.427
	Montelukast	19.0 (24)	13.8 (8)	12.5 (2)	0.724	1 vs 2 vs 3	–
	Dapsone	3.2 (4)	27.6 (16)	50.0 (8)	**<0.001** **<0.001** **<0.001**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.438 0.364 0.532
	Analgesics	5.6 (7)	22.4 (13)	31.3 (5)	**<0.001** **0.001** **0.005**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.282 0.252 0.292
	Methotrexate	2.4 (3)	17.2 (10)	12.5 (2)	**0.001** **0.001**	1 vs 2 vs 3 1 vs 2	0.258 0.269
	Colchicine	1.6 (2)	13.8 (8)	12.5 (2)	**0.002** **0.002**	1 vs 2 vs 3 1 vs 2	0.243 0.250
	Cyclophosphamide	0.8 (1)	3.4 (2)	6.3 (1)	0.099	1 vs 2 vs 3	–
	Canakinumab	0.0 (0)	1.7 (1)	12.5 (2)	**0.006** **0.012**	1 vs 2 vs 3 1 vs 3	0.274 0.335
	Pentoxifylline	0.8 (1)	0.0 (0)	12.5 (2)	**0.017** **0.034** **0.044**	1 vs 2 vs 3 1 vs 3 2 vs 3	0.268 0.257 0.317
	Polidocanol	0.8 (1)	0.0 (0)	6.3 (1)	0.237	1 vs 2 vs 3	–
	Anakinra	0.0 (0)	0.0 (0)	6.3 (1)	0.080	1 vs 2 vs 3	–
Clinical symptoms at disease onset, % (n of 232)	**Wheals, rash**	96.0 (121)	94.8 (55)	93.8 (15)	0.641	1 vs 2 vs 3	–
	Itching	88.9 (112)	77.6 (45)	62.5 (10)	**0.009** **0.044** **0.012**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.215 0.148 0.240
	Angioedema	42.9 (54)	39.7 (23)	43.8 (7)	0.910	1 vs 2 vs 3	–
	Burning of the skin	24.6 (31)	43.1 (25)	25.0 (4)	**0.037** **0.011**	1 vs 2 vs 3 1 vs 2	0.183 0.187
	Post-inflammatory hyperpigmentation	7.1 (9)	32.8 (19)	43.8 (7)	**<0.001** **<0.001** **<0.001**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.363 0.331 0.366
	Lethargy, fatigue	8.7 (11)	24.1 (14)	18.8 (3)	**0.014** **0.005**	1 vs 2 vs 3 1 vs 2	0.202 0.209
	Pain of the skin	7.1 (9)	29.3 (17)	37.5 (6)	**<0.001** **<0.001** **0.002**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.320 0.296 0.312
	Joint swelling/ pain	4.8 (6)	13.8 (8)	18.8 (3)	**0.024** **0.040**	1 vs 2 vs 3 1 vs 2	0.180 0.158
	Fever, chills	7.9 (10)	8.6 (5)	12.5 (2)	0.778	1 vs 2 vs 3	–
	Muscle/ bone aches	4.0 (5)	8.6 (5)	6.3 (1)	0.353	1 vs 2 vs 3	–
	Eye redness/ inflammation	3.2 (4)	8.6 (5)	18.8 (3)	**0.031** **0.031**	1 vs 2 vs 3 1 vs 3	0.188 0.227
	Abdominal complaints	3.2 (4)	6.9 (4)	12.5 (2)	0.130	1 vs 2 vs 3	–
	Others	9,5 (12)	3.4 (2)	6.3 (1)	0.345	1 vs 2 vs 3	–
	Swelling of lymph node	0.8 (1)	5.2 (3)	0.0 (0)	0.159	1 vs 2 vs 3	–
Clinical symptoms ever experienced, % (n of 232)	**Wheals, rash**	100.0 (126)	100.0 (58)	100.0 (16)	1.000	1 vs 2 vs 3	–
	Itching	96.8 (122)	89.7 (52)	93.8 (15)	0.115	1 vs 2 vs 3	–
	Angioedema	61.9 (78)	65.5 (38)	75.0 (12)	0.566	1 vs 2 vs 3	–
	Burning of the skin	54.0 (68)	70.7 (41)	56.3 (9)	**0.098** **0.032**	1 vs 2 vs 3 1 vs 2	0.152 0.158

	Post-inflammatory hyperpigmentation	20.6 (26)	69.0 (40)	87.5 (14)	**<0.001** **<0.001** **<0.001**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.524 0.468 0.470
	Lethargy, fatigue	27.8 (35)	55.2 (32)	62.5 (10)	**<0.001** **<0.001** **0.005**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.290 0.265 0.236
	Pain of the skin	17.5 (22)	46.6 (27)	62.5 (10)	**<0.001** **<0.001** **<0.001**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.355 0.306 0.341
	Joint swelling/ pain	18.3 (23)	36.2 (21)	68.8 (11)	**<0.001** **0.008** **<0.001** **0.020**	1 vs 2 vs 3 1 vs 2 1 vs 3 2 vs 3	0.326 0.196 0.374 0.270
	Fever, chills	15.1 (19)	22.4 (13)	31.3 (5)	0.186	1 vs 2 vs 3	–
	Muscle/ bone aches	12.7 (16)	20.7 (12)	50.0 (8)	**0.002** **0.001** **0.028**	1 vs 2 vs 3 1 vs 3 2 vs 3	0.263 0.315 0.272
	Eye redness/ inflammation	7.1 (9)	27.6 (16)	50.0 (8)	**<0.001** **<0.001** **<0.001**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.362 0.277 0.417
	Abdominal complaints	11.9 (15)	20.7 (12)	31.3 (5)	0.066	1 vs 2 vs 3	–
	Others	17.5 (22)	12.1 (7)	12.5 (2)	0.710	1 vs 2 vs 3	–
	Swelling of lymph node	1.6 (2)	13.8 (8)	18.8 (3)	**0.001** **0.002** **0.010**	1 vs 2 vs 3 1 vs 2 1 vs 3	0.265 0.250 0.294
Body parts affected by wheals, % (n of 232)	**Lower legs**	45.2 (57)	53.4 (31)	56.3 (9)	0.475	1 vs 2 vs 3	–
	Back	50.8 (64)	44.8 (26)	62.5 (10)	0.438	1 vs 2 vs 3	–
	Arms	54.8 (69)	65.5 (38)	56.3 (9)	0.385	1 vs 2 vs 3	–
	Hands	43.7 (55)	32.8 (19)	56.3 (9)	0.174	1 vs 2 vs 3	–
	Upper legs	57.9 (73)	70.7 (41)	68.8 (11)	0.218	1 vs 2 vs 3	–
	Breast	33.3 (42)	46.6 (27)	50.0 (8)	0.142	1 vs 2 vs 3	–
	Face	37.3 (47)	31.0 (18)	56.3 (9)	0.180	1 vs 2 vs 3	–
	Neck	32.5 (41)	24.1 (14)	62.5 (10)	**0.015** **0.019** **0.004**	1 vs 2 vs 3 1 vs 3 2 vs 3	0.205 0.197 0.337
	Varying locations	34.1 (43)	25.9 (15)	18.8 (3)	0.330	1 vs 2 vs 3	–
	Feet	22.2 (28)	31.0 (18)	31.3 (5)	0.333	1 vs 2 vs 3	–
	Abdominal	21.4 (27)	31.0 (18)	25.0 (4)	0.334	1 vs 2 vs 3	–
	Lips	19.8 (25)	15.5 (9)	25.0 (4)	0.601	1 vs 2 vs 3	–
	Eyes	19.0 (24)	19.0 (11)	25.0 (4)	0.816	1 vs 2 vs 3	–
	Scalp	11.9 (15)	25.9 (15)	25.0 (4)	**0.036** **0.017**	1 vs 2 vs 3 1 vs 2	0.177 0.176
	Cheeks	10.3 (13)	17.2 (10)	18.8 (3)	0.302	1 vs 2 vs 3	–
Frequency of wheals, % (n of 214)	**daily**	21.7 (26)	21.2 (11)	23.1 (3)	0.960	1 vs 2 vs 3	–
	nearly every day	11.7 (14)	17.3 (9)	0.0 (0)	0.257	1 vs 2 vs 3	–
	several times a week	20.8 (25)	23.1 (12)	15.4 (2)	0.884	1 vs 2 vs 3	–
	several times a month	11.7 (14)	13.5 (7)	7.7 (1)	0.881	1 vs 2 vs 3	–
	irregular intervals	34.2 (41)	25.0 (13)	53.8 (7)	0.172	1 vs 2 vs 3	–
Time of the day, % (n of 227)*	**in the morning**	13.5 (17)	25.9 (15)	31.3 (5)	**0.046** **0.040**	1 vs 2 vs 3 1 vs 2	0.172 0.152

	at noon	3.2 (4)	0.0 (0)	0.0 (0)	0.507	1 vs 2 vs 3	–
	in the evening	17.5 (22)	25.9 (15)	25.0 (4)	0.355	1 vs 2 vs 3	–
	at night	17.5 (22)	31.0 (18)	12.5 (2)	0.097	1 vs 2 vs 3	–
	no specific time	57.1 (72)	50.0 (29)	56.3 (9)	0.660	1 vs 2 vs 3	–
Trigger, % (n of 151)*	**stress**	67.9 (55)	70.0 (28)	77.8 (7)	0.838	1 vs 2 vs 3	–
	infection	27.2 (22)	37.5 (15)	33.3 (3)	0.429	1 vs 2 vs 3	–
	other	30.9 (25)	27.5 (11)	22.2 (2)	0.882	1 vs 2 vs 3	–
	warmth/sweating	19.8 (16)	15.0 (6)	33.3 (3)	0.587	1 vs 2 vs 3	–
	physical exertion	14.8 (12)	15.0 (6)	22.2 (2)	0.869	1 vs 2 vs 3	–
	new medication	12.3 (10)	17.5 (7)	11.1 (1)	0.627	1 vs 2 vs 3	–
	cold	11.1 (9)	12.5 (5)	11.1 (1)	0.911	1 vs 2 vs 3	–
	UV rays	8.6 (7)	5.0 (2)	33.3 (3)	0.093	1 vs 2 vs 3	–

Table E5:

Model	Unstandardized Coefficients		Sig.	95.0% Confidence Interval for B	
	B	Std. Error		Lower Bound	Upper Bound
(Constant)	74.035	27.128	.008	19.841	128.229
Wheal_duration_more than 24h	-40.967	19.127	**.036**	-79.178	-2.756
First_manifestation_pain	10.707	18.321	.561	-25.892	47.307
First_manifestation_discoloration	-11.823	18.886	.534	-49.553	25.906
First_manifestation_pruritus	-9.364	18.593	.616	-46.507	27.779
First_manifestation_joint_swelling_pain	15.081	27.849	.590	-40.555	70.716
First_manifestation_eye_inflammation	-34.758	31.842	.279	-98.370	28.853
First_manifestation_fever	-26.169	30.383	.392	-86.867	34.528
First_manifestation_abdominal_complaints	94.954	31.408	**.004**	32.208	157.699
First_manifestation_muscle_bone_aches	15.463	31.138	.621	-46.741	77.668
First_manifestation_fatigue	-3.120	22.173	.889	-47.416	41.176
Treatment_efficacy_(antihistamines)	-1.544	19.751	.938	-41.002	37.913
Treatment_efficacy_(omalizumab)	-4.938	12.079	.684	-29.068	19.192

Table E6:

Medication	Any improvement, % (n/n)				Significant improvement, % (n/n)			
	CSU	UV	P-value	Effect size	CSU	UV	P-value	Effect size
Antihistamines	78.0 (96/123)	67.7 (67/99)	0.082	0.117	17.9 (22/123)	11.1 (11/99)	0.124	–
Oral corticosteroids	82.5 (52/63)	93.3 (56/60)	0.067	0.165	50.8 (32/63)	73.3 (44/60)	**0.009**	0.171
Omalizumab	87.8 (43/49)	64.9 (24/37)	0.011	0.273	71.4 (35/49)	40.5 (15/37)	**0.012**	0.165
Topical corticosteroids	73.1 (19/26)	50.0 (17/34)	0.071	0.233	0.0 (0/26)	11.8 (4/34)	**0.042**	0.144
Cyclosporine	89.5 (17/19)	85.0 (17/20)	1.000	–	47.4 (9/19)	55.0 (11/20)	0.382	–
(Hydroxy)chloroquine	50.0 (3/6)	54.8 (17/31)	1.000	–	16.7 (1/6)	29.0 (9/31)	**0.006**	0.189
Montelukast	70.8 (17/24)	58.3 (7/12)	0.479	–	8.3 (2/24)	16.7 (2/12)	1.000	–
Dapsone	75.0 (3/4)	56.0 (14/25)	0.622	–	50.0 (2/4)	36.0 (9/25)	**0.014**	0.162
Analgesics	42.9 (3/7)	45.5 (10/22)	1.000	–	0.0 (0/7)	22.7 (5/22)	**0.019**	0.162
Methotrexate	33.3 (1/3)	93.3 (14/15)	0.056	0.600	33.3 (1/3)	53.3 (8/15)	**0.013**	0.174
Colchicine	100.0 (2/2)	91.7 (11/12)	1.000	–	0.0 (0/2)	8.3 (1/12)	0.457	–
Cyclophosphamide	0.0 (0/1)	75.0 (3/4)	0.400	–	0.0 (0/1)	0.0 (0/4)	–	–
Pentoxifylline	100.0 (1/1)	50.0 (1/2)	1.000	–	0.0 (0/1)	50.0 (1/2)	0.457	–
Polidocanol	0.0 (0/1)	0.0 (0/1)	1.000	–	0.0 (0/1)	0.0 (0/1)	–	–
Canakinumab	0.0 (0/0)	50.0 (2/4)	1.000	–	0.0 (0/0)	0.0 (0/4)	–	–
Anakinra	0.0 (0/0)	100.0 (1/1)	1.000	–	0.0 (0/0)	0.0 (0/1)	–	–

Tests used: Chi-square test for analysis of binary variables (If the expected cell count fell below 5, Fisher's exact test was used instead). Mann–Whitney U test for independent non-parametric variables. Unpaired T-test for normally distributed data.

Table E7:

Medication, % (n of 106)	Symptoms worsened	No change	Slight improvement	Moderate improvement	Significant improvement
Antihistamines	1.0 (1)	31.3 (31)	30.3 (30)	26.3 (26)	11.1 (11)
Oral corticosteroids	0.0 (0)	6.7 (4)	6.7 (4)	13.3 (8)	73.3 (44)
Omalizumab	10.8 (4)	24.3 (9)	10.8 (4)	13.5 (5)	40.5 (15)
Topical corticosteroids	2.9 (1)	47.1 (16)	20.6 (7)	17.6 (6)	11.8 (4)
Cyclosporine	0.0 (0)	15.0 (3)	15.0 (3)	15.0 (3)	55.0 (11)
(Hydroxy)chloroquine	3.2 (1)	41.9 (13)	12.9 (4)	12.9 (4)	29.0 (9)
Montelukast	0.0 (0)	41.7 (5)	0.0 (0)	41.7 (5)	16.7 (2)
Dapsone	8.0 (2)	36.0 (9)	0.0 (0)	20.0 (5)	36.0 (9)
Analgesics	13.6 (3)	40.9 (9)	13.6 (3)	9.1 (2)	22.7 (5)
Methotrexate	0.0 (0)	6.7 (1)	13.3 (2)	26.7 (4)	53.3 (8)
Colchicine	0.0 (0)	8.3 (1)	50.0 (6)	33.3 (4)	8.3 (1)
Cyclophosphamide	0.0 (0)	25.0 (1)	0.0 (0)	75.0 (3)	0.0 (0)
Canakinumab	25.0 (1)	25.0 (1)	50.0 (2)	0.0 (0)	0.0 (0)
Pentoxifylline	0.0 (0)	50.0 (1)	0.0 (0)	0.0 (0)	50.0 (1)
Polidocanol	0.0 (0)	100.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Anakinra	0.0 (0)	0.0 (0)	0.0 (0)	100.0 (1)	0.0 (0)

Table E8:

Medication, % (n of 126)	Symptoms worsened	No change	Slight improvement	Moderate improvement	Significant improvement
Antihistamines	0.0 (0)	22.0 (27)	43.1 (53)	17.1 (21)	17.9 (22)
Oral corticosteroids	3.2 (2)	14.3 (9)	12.7 (8)	19.0 (12)	50.8 (32)
Omalizumab	4.1 (2)	8.2 (4)	6.1 (3)	10.2 (5)	71.4 (35)
Topical corticosteroids	3.8 (1)	23.1 (6)	57.7 (15)	15.4 (4)	0.0 (0)
Cyclosporine	0.0 (0)	10.5 (2)	26.3 (5)	15.8 (3)	47.4 (9)
(Hydroxy)chloroquine	0.0 (0)	50.0 (3)	16.7 (1)	16.7 (1)	16.7 (1)
Montelukast	0.0 (0)	29.2 (7)	29.2 (7)	33.3 (8)	8.3 (2)
Dapsone	0.0 (0)	25.0 (1)	0.0 (0)	25.0 (1)	50.0 (2)
Analgesics	0.0 (0)	57.1 (4)	42.9 (3)	0.0 (0)	0.0 (0)
Methotrexate	0.0 (0)	66.7 (2)	0.0 (0)	0.0 (0)	33.3 (1)
Colchicine	0.0 (0)	0.0 (0)	100.0 (2)	0.0 (0)	0.0 (0)
Cyclophosphamide	0.0 (0)	100.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Pentoxifylline	0.0 (0)	0.0 (0)	100.0 (1)	0.0 (0)	0.0 (0)
Polidocanol	0.0 (0)	0.0 (0)	100.0 (1)	0.0 (0)	0.0 (0)

Repository E Figure No.1

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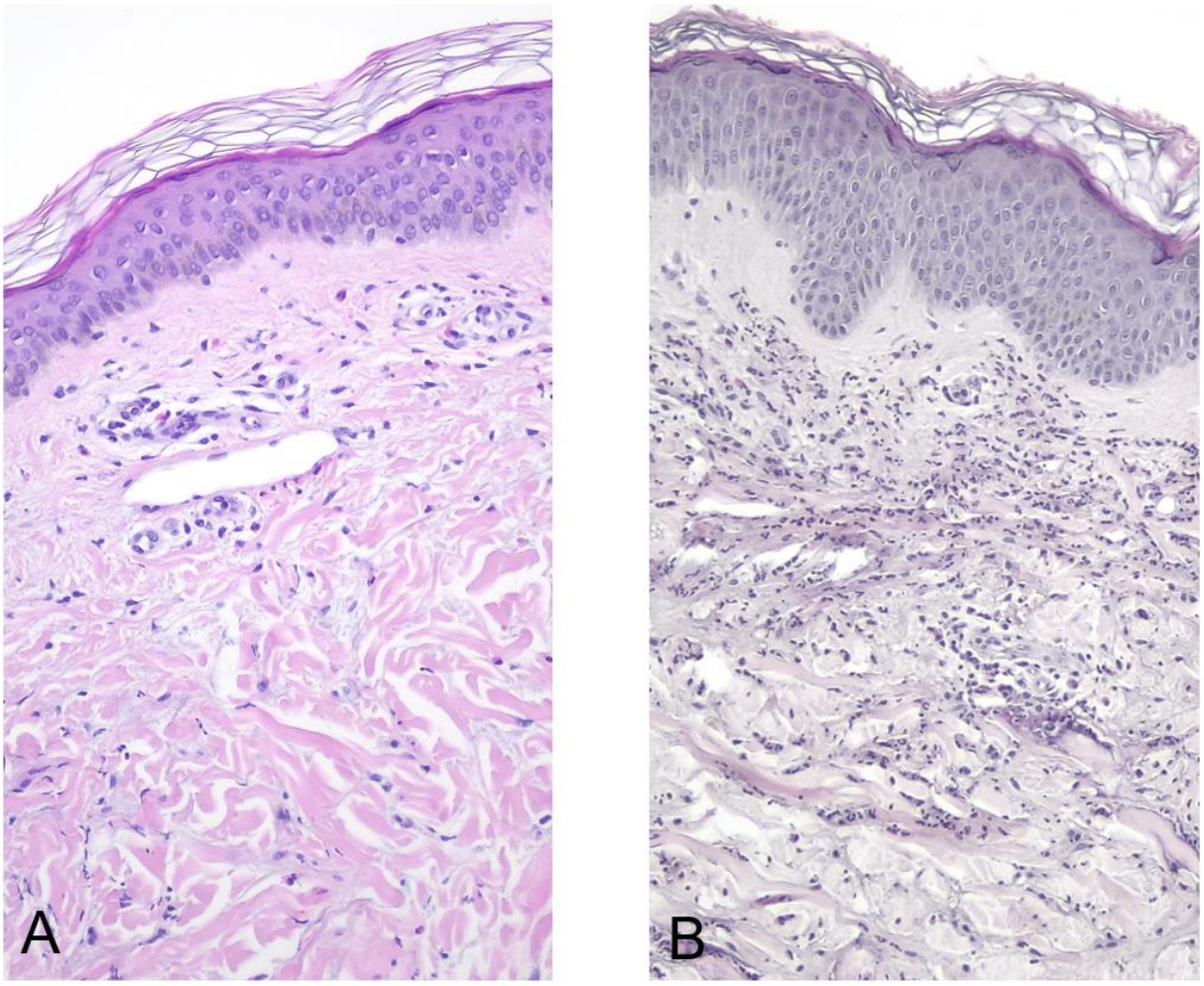


UVERSICU

Questionnaire – URTICARIA/URTICARIAL VASCULITIS

I. General Information

Please check the diagnosis which applies:

☐ chronic spontaneous urticaria or ☐ urticarial vasculitis

Code_Number: _____

Szusagen

Date of completion: _____

sex: ☐ female ☐ male

weight: _____kg height: _____m

Age:

II. Questions on natural history and disease course

1. When did you first notice the symptoms of urticaria/ urticarial vasculitis? (Month/Year)? _____ . _____

2. Which symptoms occurred first? (Please check all that apply)

- ☐ wheals, rash
- ☐ itching
- ☐ burning of the skin
- ☐ pain of the skin
- ☐ discoloration of skin (postinflammatory hyperpigmentation)
- ☐ skin swelling (angioedema)
- ☐ lethargy, fatigue, generally feeling ill
- ☐ fever, chills
- ☐ abdominal complaints (nausea, vomiting)
- ☐ swelling of lymph node
- ☐ muscle/ bone aches
- ☐ joint swelling/ pain
- ☐ eye redness/ inflammation
- ☐ others, please explain:_____

3. In your view, does a trigger for the appearance of the disease exist?

☐ no ☐ yes

If yes, which ones?

- ☐ infection
- ☐ stress
- ☐ new medication for the treatment of a different disease

- ☐ physical exertion
- ☐ cold/warmth/sweating
- ☐ sun rays/ UV rays
- ☐ other trigger: _____

4. When were you first diagnosed with urticaria/urticarial vasculitis? (Month/Year)?____. _____

5. Please list all complaints that have – at any point in time - occurred in the context of your urticaria/urticarial vasculitis

- ☐ wheals, rash
- ☐ itch
- ☐ burning of the skin
- ☐ pain of the skin
- ☐ discoloration of skin (postinflammatory hyperpigmentation)
- ☐ skin swelling (angioedema)
- ☐ lethargy, fatigue, general feeling of being ill
- ☐ fever, chills
- ☐ abdominal complaints (nausea, vomiting)
- ☐ lymph node swelling
- ☐ muscle/ bone aches
- ☐ joint swelling/ pain
- ☐ eye redness/ inflammation
- ☐ others, please explain: _____

6. Which symptoms are **currently** occuring?

- ☐ wheals, rash
- ☐ itch
- ☐ burning of the skin
- ☐ pain of the skin
- ☐ discoloration of skin (postinflammatory hyperpigmentation)
- ☐ skin swelling (angioedema)
- ☐ lethargy, fatigue, general feeling of being ill
- ☐ fever, chills
- ☐ abdominal complaints (nausea, vomiting)
- ☐ lymph node swelling
- ☐ muscle / bone aches
- ☐ joint swelling/ pain
- ☐ eye redness/ inflammation
- ☐ others, please explain:

7. How long do the wheals last? If a swelling of the skin (angioedema) occurs, how long does it last?

Wheals:

- ☐ <1h
- ☐ 1-6h
- ☐ 6-12h
- ☐ 12h
- ☐ 12-24h
- ☐ 24h
- ☐ 24-48h
- ☐ 48h
- ☐ 48-72h
- ☐ 72h
- ☐ >72h

Swelling of the skin (angioedema):

- ☐ <1h
- ☐ 1-6h
- ☐ 6-12h
- ☐ 12h
- ☐ 12-24h
- ☐ 24h
- ☐ 24-48h
- ☐ 48h
- ☐ 48-72h
- ☐ 72h
- ☐ >72h

8. How often do you currently experience wheals?

- ☐ daily
- ☐ nearly every day
- ☐ several times a week
- ☐ several times a month
- ☐ at irregular intervals, approximately:

9. At what time do the wheals mainly occur?

☐ in the morning ☐ at noon ☐ in the evening ☐ at night ☐ no specific time

10. In your view, is there a certain season in which the wheals occur?

☐ no ☐ maybe ☐ yes, namely: _____

11. Which body parts are mainly affected by the wheals?

- ☐ face
- ☐ eyes
- ☐ lips
- ☐ cheeks
- ☐ scalp
- ☐ neck
- ☐ arms
- ☐ hands

- ☐ breast
- ☐ back
- ☐ upper legs
- ☐ lower legs
- ☐ feet
- ☐ different body parts

12. Are there trigger factors that can cause a relapse of the disease?

☐ no ☐ yes

If yes, which ones?

- ☐ infection
- ☐ stress
- ☐ new medication taken for the treatment of a different disease
- ☐ physical exertion
- ☐ cold/warmth/sweating
- ☐ sun rays/ UV rays
- ☐ other trigger: _____

13. Did you notice a food allergy/ intolerance?

☐ no ☐ yes, namely: _____

14. Do you have any allergies/ intolerances?

☐ no ☐ yes, namely: _____

15. Do you have any other skin diseases?

☐ no ☐ yes, namely: _____

16. Do you have any other (chronic) diseases?

- ☐ cardiovascular disease
- ☐ lung disease
- ☐ liver disease
- ☐ kidney disease

- ☐ metabolic disease
- ☐ cancer
- ☐ autoimmune disease
- ☐ rheumatologic disease
- ☐ mental illness
- ☐ others, namely: ___
- ☐ I don't have/had any of these diseases.

17. Which diseases do/did your grandparents/parents/siblings suffer from?

- ☐ urticarial vasculitis, chronic spontaneous
- ☐ urticaria food allergy/ intolerance
- ☐ other allergies/ intolerances
- ☐ other skin diseases
- ☐ autoimmune/ rheumatologic diseases
- ☐ others, please specify: _____

III. Questions on treatment

18. Which therapy do you **currently** receive for your urticaria/urticarial vasculitis? (Multiple answers possible)

- ☐ antihistamines (e.g. Loratadin®, Ebastin®, Telfast®, Aerius®, Urtimed®)
- ☐ steroid cream(e.g. Prednitop®, Elocom®, Monovo®)
- ☐ Pentoxifylline(Trental®)
- ☐ Polidocanol (Thesit®)
- ☐ oral steroids (e.g. Decortin®, Urbason®)
- ☐ Cyclosporine (Immunosporin®)
- ☐ Omalizumab (Xolair®)
- ☐ Diaminodiphenylsulfon (Dapson-Fatol®)
- ☐ Hydroxychloroquin (Quensyl®)
- ☐ Chloroquin (Resochin®)
- ☐ pain killers (z.B. Ibuprofen, Arcoxia®)
- ☐ Anakinra (Kineret®)
- ☐ Canakinumab (Ilaris®)
- ☐ Montelukast (Singulair®)
- ☐ Methotrexat - MTX (Bendatrexat®)
- ☐ Cyclophosphamid (Endoxan®)
- ☐ Colchicin (Colchicum-Dispert®)
- ☐ Interferon Alpha (Roferon®)
- ☐ Others, please specify: _____

19. How would you describe the results of your current urticaria/urticarial vasculitis treatment?

- [ ] good success (symptom decline at least
- [ ] 90%) partial success (symptom decline <90%)
- [ ] no symptom decline (<30%)

20. Which of the following drugs **have you ever taken** for the treatment of your urticaria/ urticarial vasculitis? How effective were they?

Treatment	Symptoms worsened	No change	Slight change	Moderate change	Significant change
Antihistamines (e.g. Loratadin®, Ebastin®, Telfast®, Aerius®, Urtimed®)	☐	☐	☐	☐	☐
Steroid cream (e.g. Prednitop®, Elocom®, Monovo®)	☐	☐	☐	☐	☐
Pentoxifylline (Trental®)	☐	☐	☐	☐	☐
Polidocanol (Thesit®)	☐	☐	☐	☐	☐
Oral steroids (Decortin®, Urbason®)	☐	☐	☐	☐	☐
Cyclosporine (Immunosporin®)	☐	☐	☐	☐	☐
Omalizumab (Xolair®)	☐	☐	☐	☐	☐
Diaminodiphenylsulfon (Dapson-Fatol®)	☐	☐	☐	☐	☐
Hydroxychloroquin (Quensyl®) or Chloroquin (Resochin®)	☐	☐	☐	☐	☐
Pain killers (e.g. Ibuprofen, Arcoxia®)	☐	☐	☐	☐	☐
Anakinra (Kineret®)	☐	☐	☐	☐	☐
Canakinumab (Ilaris®)	☐	☐	☐	☐	☐
Montelukast (Singulair®)	☐	☐	☐	☐	☐
Methotrexat - MTX (Bendatrexat®)	☐	☐	☐	☐	☐
Cyclophosphamid (Endoxan®)	☐	☐	☐	☐	☐
Colchicin (Colchicum-Dispert®)	☐	☐	☐	☐	☐
Interferon Alpha (Roferon®)	☐	☐	☐	☐	☐
Others, please specify: _____					

21. Have you experienced any side effects while taking the following medication? If yes, please specify. Did you have to stop taking a medication because of side effects?

Treatment	No side effects	Type of side effect (short description)	Discontinued because of side effect
Antihistamines (e.g. Loratadin®, Ebastin®, Telfast®, Aerius®, Urtimed®)	☐		☐
Steroid cream (e.g. Prednitop®, Elocom®, Monovo®)	☐		☐
Pentoxifylline (Trental®)	☐		☐
Polidocanol (Thesit®)	☐		☐
Oral steroids (Decortin®, Urbason®)	☐		☐
Cyclosporine (Immunosporin®)	☐		☐
Omalizumab (Xolair®)	☐		☐
Diaminodiphenylsulfon (Dapson-Fatol®)	☐		☐
Hydroxychloroquin (Quensyl®) or Chloroquin (Resochin®)	☐		☐
Pain killers (Ibuprofen, Arcoxia®)	☐		☐
Anakinra (Kineret®)	☐		☐
Canakinumab (Ilaris®)	☐		☐
Montelukast (Singulair®)	☐		☐
Methotrexat - MTX (Bendatrexat®)	☐		☐
Cyclophosphamid (Endoxan®)	☐		☐
Colchicin (Colchicum-Dispert®)	☐		☐
Interferon Alpha (Roferon®)	☐		☐

IV. Questions regarding quality of life

22. Are you currently limited in your general efficiency because of your urticaria/ urticarial vasculitis?

☐ not at all ☐ barely ☐ moderately ☐ severely ☐ very severely

23. If your urticaria/ urticarial vasculitis has an impact on your current performance at work, by how many percent is your efficiency diminished?
(e.g. 0% no restriction und 100% complete loss of efficiency)?

_____% percentage of limitation of efficiency at work

☐ Not applicable, I am not currently working

24. In the past, were you unable to work because of your urticaria/ urticarial vasculitis?

☐ no ☐ yes

If yes, how many days in the last 12 months?_____days

V. For women

25. Do you see a connection between an aggravation of your urticaria/urticarial vasculitis and your period?

☐ not applicable, no period
☐ no
☐ yes, please specify: _____

VI. Additional experiences / remarks

If you have any others experiences, complaints or other remarks concerning urticaria/ urticarial vasculitis, please feel free to comment on them below.

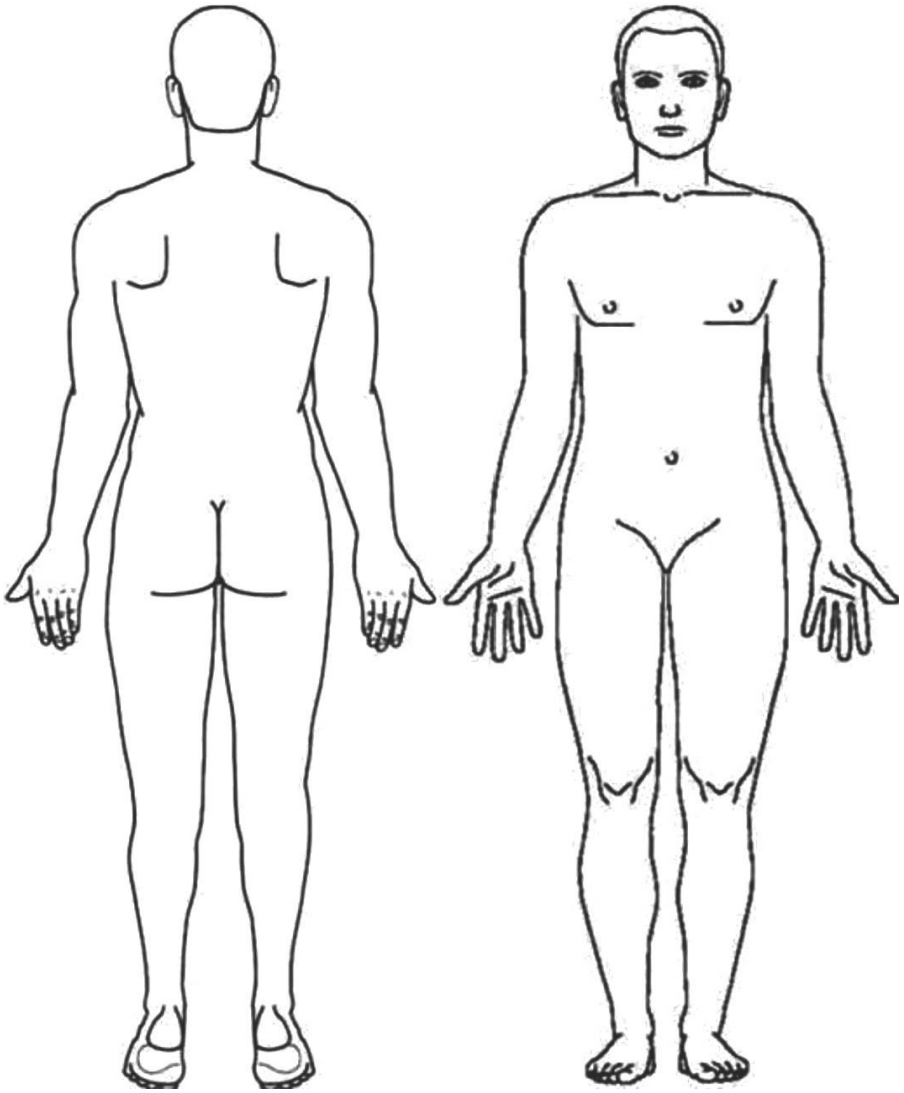
_____

_____

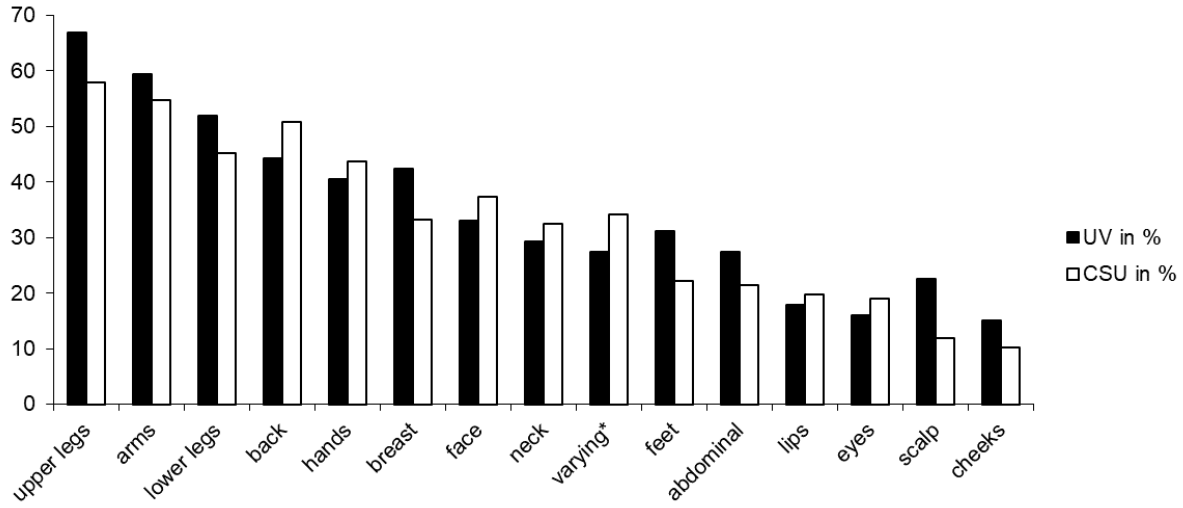
Thanks a lot for your support!

VII. Images

Please paint in the body parts, where the wheals mainly occur.



A)



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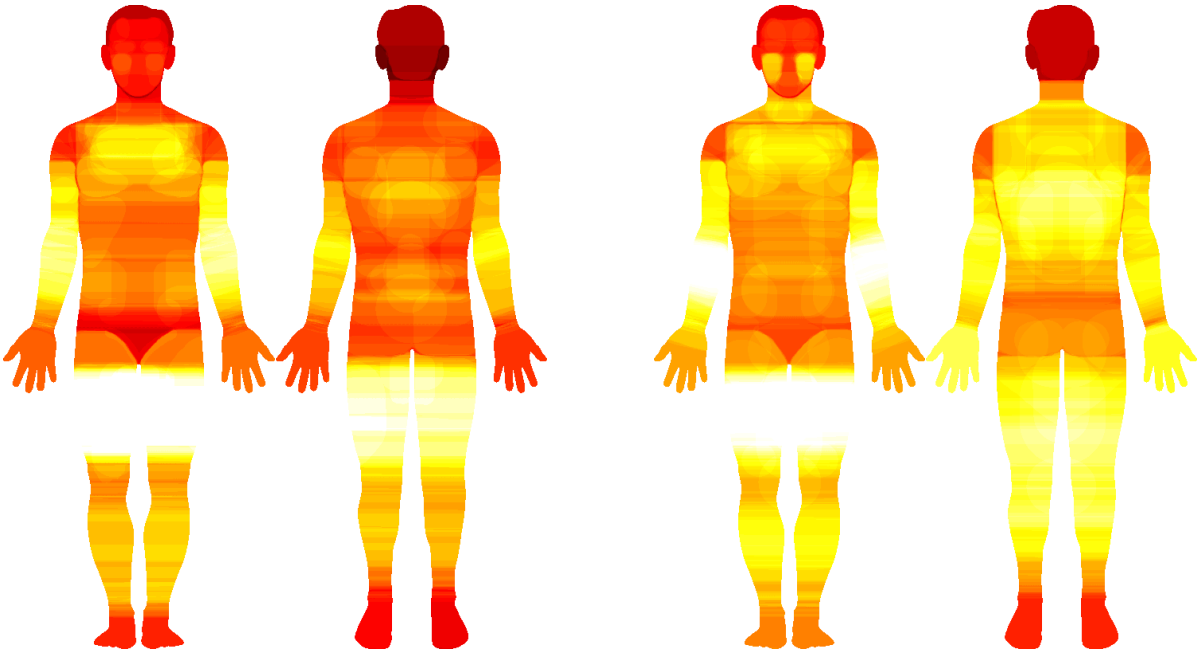

Urticarial vasculitis (UV) **Chronic spontaneous urticaria (CSU)**

8% 61%