

ORIGINAL ARTICLE

Selected urticaria patients benefit from a referral to tertiary care centres – results of an expert survey

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Abstract

Background Urticaria is a frequent reason for consultations. Recently, it has been demonstrated that the management of chronic spontaneous urticaria (csU) in the practice setting does not fully comply with published guidelines. In addition, it was shown that one of four csU patients is referred to specialized centres.

Objective To analyse the management of urticaria patients in tertiary referral centres.

Methods During a standardized expert-to-expert interview, 41 specialists from German tertiary care centres were asked for different aspects of urticaria patient care with a special focus on csU.

Results On average, the participating centres saw 25 csU patients per month. All ran programmes for the identification of underlying causes with an average success rate of $45 \pm 3\%$ which is considerably higher as has been found in the practice setting. In those patients where an identification succeeds, infections, drugs, intolerance and autoreactivity were reported to be causes in 41%, 20%, 17% and 16%. In their symptomatic treatment the majority of centres (71%) followed the guidelines by using regular dosed non-sedating H₁-antihistamines as first line and higher doses (61%) as second line option. In contrast to the practice setting, meaningful experience also existed for alternative therapies in antihistamine-resistant patients, such as dapsone, cyclosporin and omalizumab. The expenditure of time, laboratory costs and frequency of follow-up visits was reported to be above average in case of csU.

Conclusion This study indicates that some urticaria patients, especially those with unknown causes or with an H₁-antihistamine-resistant disease, may benefit from a referral to tertiary care centres.

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Conflict of interest

The authors disclose the following relevant interactions with pharmaceutical industry: *K. Weller*: The author declares that he is or recently was compensated for educational lectures by Essex Pharma (now MSD), Novartis and UCB. *N. Schoepke*: None. *K. Krause*: The author declares that she is or recently was compensated for educational lectures by Novartis and Uriach. *E. Ardelean*: None. *M. Bräutigam*: The author is employee at Novartis Pharma GmbH. *M. Maurer*: The author declares that he is or recently was a Speaker and/or Advisor for Almirall Hermal, Essex Pharma, Merckle Recordati, Novartis, Sanofi Aventis, Schering-Plough, MSD, Merck, UCB, and Uriach.

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Introduction

Urticaria is characterized by the recurrent and sudden appearance of itchy weals and/or angioedema. The current guidelines^{1,2} distinguish several subtypes, i.e. spontaneous urticaria (acute and chronic), physical urticaria (e.g. dermographic urticaria and cold contact urticaria) and other urticaria types (e.g. cholinergic urticaria). Although good quality evidence is lacking for most of the subtypes regarding their prevalence, natural course and response

to treatment, epidemiological data for chronic spontaneous urticaria (csU) show that 0.5–1% of the general population is affected at any single time, thus demonstrating its high importance in health care.³ Furthermore, studies on the quality of life and on the socioeconomic impact of urticaria revealed a high disease burden^{4–6} and considerable direct and indirect health care costs.^{7,8}

The guidelines for the management of urticaria² suggest the identification and treatment of underlying causes in csU if

possible. However, as yet, there is no reliable data on how often this is actually possible. As symptomatic therapy, H1-antihistamines are the only licensed option. Since a considerable proportion does not respond sufficiently to these drugs in regular doses³ the guidelines recommend a step up therapy approach in these patients, including an up dosing or change of the H1-antihistamine, the addition of H2-blockers or leukotriene-antagonists or the application of cyclosporin, dapsone or omalizumab.² For most of these options, good quality evidence regarding their efficacy is missing. A short course of systemic corticosteroids may be applied to cope exacerbations of csU for 3–7 days.²

It is important to note that most of the available information on the natural history, causes and treatment effects in urticaria patients was generated in controlled study settings or by the retrospective analysis of medical records of single expert centres rather than in the normal situations at a GP, dermatologist or paediatrician. Accordingly, its validity for the real life health care setting might be limited. For this reason, we recently performed a nationwide German study in a population of more than 750 GPs, dermatologists and paediatricians in private practice.^{9,10} We found a high number of consultations due to urticaria and that an underlying cause of csU was only rarely found. The diagnostic work up as well as the therapeutic management was only partly in accordance with the guideline recommendations.¹⁰ Furthermore, the data revealed that care for these patients was rated as time consuming and expensive and that the patients were perceived as a group with high expectations that is difficult to satisfy. Interestingly, the study also found that around every third patient is referred to a tertiary care centre.⁹

To work successfully towards an improvement of care it is critical to understand the entire situation of care, i.e. not only the practice setting but also the tertiary referral centre level. Accordingly, we decided to perform a survey to answer the following questions: How many and what kind of patients with urticaria are seen in tertiary referral centres? How often and which underlying causes are found? Is the search for underlying causes more successful at the tertiary care level as compared to the private practice setting? What is the therapeutic management in tertiary referral centres and what problems might affect the care of urticaria patients?

Methods

Objectives

The main objectives of this study were to obtain data on: (i) the frequency of consultations; (ii) the natural course; (iii) the diagnostic approach; (iv) the therapeutic proceeding; and (v) the general situation of medical care regarding the urticaria patient population in tertiary referral centres.

Hypotheses

The main hypotheses of the study included: (i) csU and other urticaria subtypes are of high relevance in tertiary referral centres;

(ii) different urticaria subtypes predominate in different age groups and exhibit a different course of disease; (iii) tertiary referral centres perform a different diagnostic setup as compared to primary and secondary carers; (iv) tertiary referral centres perform a different therapeutic proceeding as compared to primary and secondary carers; and (v) care of urticaria patients faces problems on various fields.

Development of the survey questions

The survey questions were developed by a panel of urticaria experts of the urticaria specialty clinic of the Department of Dermatology and Allergy of the Charité – Universitätsmedizin Berlin after a thorough literature review had been performed. Many questions were adopted from the CUBA survey (Chronische Urtikaria – Bundesweite Aerztebefragung) that has been performed earlier in a group of more than 750 physicians in the private practice setting to assure the comparability of the results.^{9,10} This process resulted in a final written form questionnaire consisting of 77 structured questions, mostly involving Likert-scale ratings, quantitative questions, yes/no lists and multiple choice questions (survey questions may be provided upon request). The topics of the questions included: (i) general questions concerning the participating experts and their departments; (ii) general questions regarding urticaria patients (such as patient numbers, frequency of the urticaria subtypes, course of the disease, gender and age); (iii) questions on the diagnostic proceeding and its success in urticaria; (iv) questions on the therapeutic management; and (v) questions regarding the situation and level of medical care for urticaria patients. Before the actual onset of the study, the survey was pretested for face validity, comprehensibility and feasibility in a test interview that led to minor changes of the wording to increase the clarity and accuracy of the questions.

Recruitment

This nationwide survey study was conducted between October 2009 and August 2010. In total, on the basis of a published list of the German Society of Dermatology, a broad sample of 103 German hospital based dermatology departments ($n = 103$) were provided a letter of invitation and information. As is typical of activities in which expert opinions are obtained, selection of experts was non-random. Therefore it is possible that the results do not fully represent all German dermatological centres. However, during the selection of this sample, special attention was paid to the fact that centres of all German regions (federal states) as well as of different sizes and focus (university and non-university hospitals) were among the addressees. Of these, 48 consented and 12 refused to participate. Forty-three did not respond to the recruitment letter. Finally, 41 dermatological centres took part in the study (participation rate 40%). In case of the remaining seven departments, which originally claimed to be interested, scheduling an appointment for the survey failed due to various reasons, such as sickness ($n = 1$), unattainability ($n = 4$) or pregnancy of the

designated participants ($n = 2$). Since the target number of experts for this survey was 40, no further efforts were made to recruit these remaining or additional centres into the study.

Procedures and study design

This expert-to-expert survey was performed as a standardized, cross-sectional, telephone-based interview. All participants were strictly asked the same questions (with the same answer options) in the same order based on the above-mentioned, previously developed questionnaire. This questionnaire was provided to all participants some days before the telephone interview. However, they were not explicitly requested to study the survey questions before the actual phone conversation took place. The time frame for each structured interview was 2 h. All interviews were performed by the same three urticaria experts (Elena Ardelean, Karoline Krause and Karsten Weller) of the Department of Dermatology and Allergy of the Charité – Universitätsmedizin Berlin. After completion of the survey every participant received 150 Euro as a financial allowance.

Statistical analysis

All responses obtained during the interviews were initially documented in the written form questionnaires. Later, these data were transferred into an electronic databank (PASW Statistics 18.0). Quality control was performed by visual inspection and descriptive analyses checking for out-of-range values. Descriptive statistics (mean, standard deviation, proportions), and graphical representations were employed to summarize and analyse the data.

Results

Participating centres

A total of 41 clinical experts of hospital based dermatology departments from all over Germany (of 14 of the 16 German federal states) participated in this expert survey. Twenty were employed in university hospitals, whereas the other 21 were based in non-university clinics. Thirty-eight (93%) of the participating centres operated an outpatient department in addition to an inpatient care. The mean number of hospital beds was 49.3 ± 21.6 .

Those 55 centres that did not respond either to the recruitment letter or refused participation were also widely distributed throughout Germany (located in 15 of the 16 federal states) and consisted of 15 university hospitals and 40 non-university clinics.

Epidemiological data

On average, the participating experts (hospitals) stated to care for 52.0 ± 47.4 urticaria patients per month, about half of them (25.4 ± 27.6) csU patients (Fig. 1). The reported number of children with csU was comparably low (2.8 ± 5.3). Asked for the frequency of patients suffering from physical urticaria or cholinergic urticaria, most hospitals were not able to report exact numbers but provided a ranking instead. Here, the majority (73%) rated

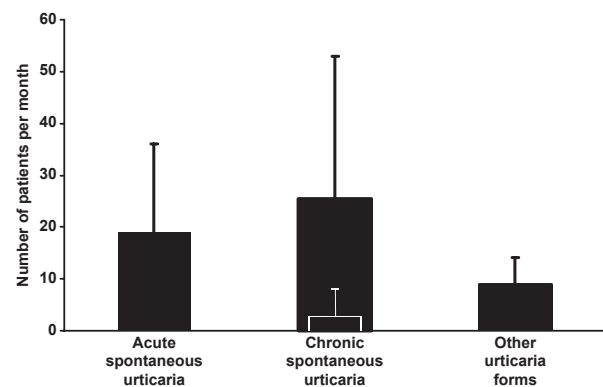


Figure 1 The participating experts were asked to estimate the number of patients with the indicated diseases that are treated in their centre every month. The results are expressed as mean $\pm$ SD. 'Other urticaria forms' were further defined as 'e.g. physical urticaria subtypes, cholinergic urticaria, contact urticaria'. The white column represents the number of children (age 6–12 years) with chronic spontaneous urticaria per month.

urticaria factitia to be the most common whereas the remaining 27% chose other disorders. As the second most common subtype, delayed pressure urticaria and cholinergic urticaria were named most often (by 39% and 27% of the participants).

In addition to patient numbers, the hospitals were asked for gender distribution, mean age of patients and mean disease duration of the different urticaria subtypes (Table 1). Although the participants reported a preponderance of women in case of acute spontaneous urticaria (58.1%) and csU (67.1%), the proportions of both genders were stated to be evenly distributed in physical urticaria, cholinergic urticaria and, notably, also in children with csU. The mean age of patients was indicated to be highest in csU (40.9 years) and considerably lower in the other forms. The mean duration of disease was perceived to be much longer in physical (43.4 months) and cholinergic urticaria (40.4 months) as compared to csU (26.3 months). Interestingly, children between 6 and 12 years of age were reported to be affected for shortest duration (10.8 months).

Chronic spontaneous urticaria was reported to be by far the most common chronic form of urticaria seen in the expert centres. Asked for the disease activity of these patients, the participants reported $15.4 \pm 11.5\%$ as mildly, $43.0 \pm 20.8\%$ as moderately and $41.6 \pm 27.0\%$ as severely affected. $28.3 \pm 20.1\%$ were stated to suffer from angioedema and $7.2 \pm 7.2\%$ to experience dyspnoea. On average, csU was reported to persist for 8.2 ± 5.3 months and patients to be seen by 2.1 ± 0.7 physicians before the first consultation.

Diagnosis

According to the current guidelines,² it is recommended to search for an underlying cause of csU to enable a causal treatment if

Table 1 The participating experts were asked to estimate the gender distribution, mean age and overall disease duration of the indicated diseases. The results are expressed as mean $\pm$ SD

Urticaria form	Gender (F : M)	Mean age	Mean duration
Acute spontaneous urticaria	58.1 $\pm$ 7.3 : 41.9 $\pm$ 7.3	31.6 $\pm$ 7.0 years	15.4 $\pm$ 1.6 days
Chronic spontaneous urticaria	67.1 $\pm$ 8.5 : 32.9 $\pm$ 8.5	40.9 $\pm$ 7.1 years	26.3 $\pm$ 3.5 months
Chronic spontaneous urticaria in children (6–12 years)	52.8 $\pm$ 6.1 : 47.2 $\pm$ 6.1	Not applicable	10.8 $\pm$ 2.0 months
Physical urticaria	53.6 $\pm$ 9.3 : 46.4 $\pm$ 9.3	33.6 $\pm$ 6.4 years	43.4 $\pm$ 6.0 months
Cholinergic urticaria	49.7 $\pm$ 14.0 : 50.3 $\pm$ 14.0	28.0 $\pm$ 5.5 years	40.4 $\pm$ 5.6 months

possible. Most of the participating centres were familiar with the guidelines (95%) and all reported to search for underlying causes in 97% of their patients by applying a broad spectrum of measures (Fig. 2). Notably, the hospitals reported to be successful in 45% of cases and infections to be the most frequent cause (in 41% of those patients where an identification was possible) (Fig. 3). In contrast, the experts indicated to find an underlying cause in only 18% and 14% of their patients with physical and cholinergic urticaria.

Treatment

Symptomatic treatment is the cornerstone of therapy in all urticaria patients where an underlying cause cannot be found or eliminated. The symptomatic therapy behaviour of the participating hospitals is shown in Fig. 4. The majority of centres followed the current guidelines by using non-sedating antihistamines (nsAHs) in regular doses as first-line treatment (70.7%) and up dosing of

nsAHs as second line option (61.0%). Oral steroids were stated to be applied very infrequently.

The efficacy of therapy is of major importance for the patients and their treating physicians. Remarkably, the participating centres reported that only 32.1 $\pm$ 21.7% of patients can be treated satisfactorily with nsAHs in regular doses but that this is the case in 69.8 $\pm$ 16.6% in case of up dosing. The figures for a combination of nsAHs in high doses with a leukotriene antagonist or with a histamine-2-receptor blocker were 58.0 $\pm$ 25.5% and 65.2 $\pm$ 17.7%, respectively. However, not all centres had experience with the latter treatment options. For the interpretation of this data it is important to keep in mind that under normal conditions only those patients who did not respond sufficiently to the previous treatment had a step up in their therapy.

In summary, these figures suggest that the guideline recommended first-, second- and third-line treatment seems to be of

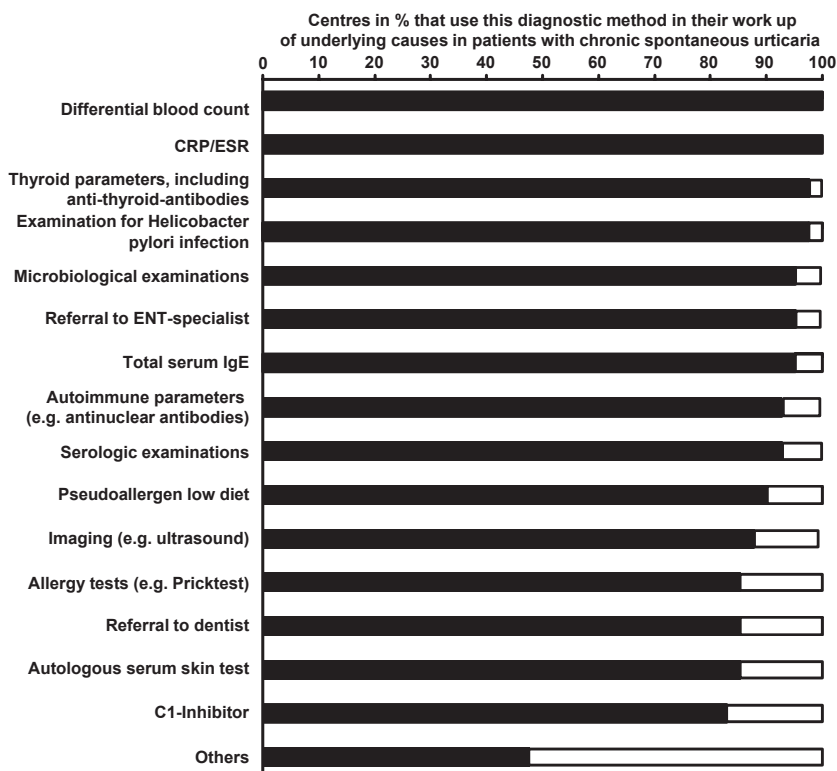


Figure 2 The participating experts were asked for the examinations performed or arranged by their centre to identify underlying causes of chronic spontaneous urticaria in their patients. All experts were requested to pick all applicable answer options. The results are expressed as the proportion of centres that chose the different options.

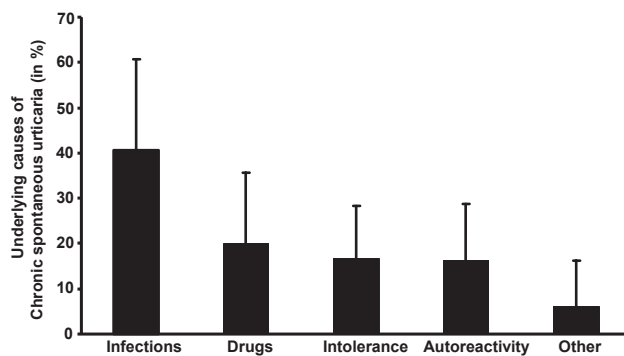


Figure 3 The participating experts were asked to distribute their patients (100%) to cause categories where an identification of an underlying cause succeeds. Given cause categories were 'infections', 'drugs', 'intolerance', 'autoreactivity' and 'other'. All columns represent the mean proportion of patients' $\pm$ SD distributed to the different answer options.

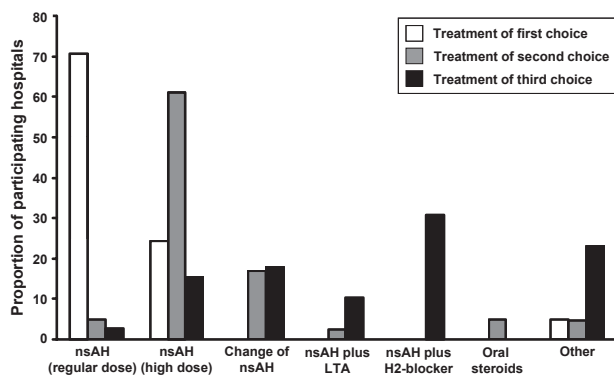


Figure 4 The participating experts were asked for their symptomatic treatment of first, second and third choice for chronic spontaneous urticaria patients (nsAH = non-sedating antihistamine, LTA = leukotriene antagonist). The results are expressed as the proportion of centres that chose the respective answer options.

benefit for many patients. However, there is a considerable proportion that cannot be sufficiently controlled by these options. Therefore, the participants were also asked for their experience with other therapeutic possibilities (Fig. 5). Although dapsons and oral steroids were reported to be most frequently used, the best evaluation regarding efficacy and side-effect profile was given for omalizumab, the least often applied therapy.

Problems concerning medical care of csU patients

The participating hospitals were asked to compare the general conditions in csU patient care to those in their other patients. Notably, the expenditure of time, laboratory costs and frequency of follow-up visits were reported to be above average in case of csU by 75.6%, 73.2% and 43.2% (Fig. 6). In contrast, the drug

costs were stated as not high by the majority of experts (80%). In a further set of questions the hospitals were asked for characteristics of csU patients that might affect care. Interestingly, 65.9% regarded the patient guidance to be difficult, 63.4% reported prevalent psychiatric comorbidities to be above average, 85.4% perceived the patients' expectations to be high and 58.5% felt that it is difficult to satisfy csU patients.

The general situation of care for csU patients was rated to be fair or not sufficient by 24.4% and 29.3%, the options, good and satisfactory were chosen by 12.2% and 34.1%. None of the participants rated the situation to be optimal. Importantly, 61.0% reported problems at the interface between care at the centres and the following care at the practice level, such as the discontinuation of the centre recommended therapies.

Although there seem to exist many factors that might hamper care, 20 of the 41 participating experts stated to be above average motivated to care for csU patients, whereas only two experts stated to be motivated below average.

Discussion

Previous studies have analysed the management of urticaria patients in the practice setting^{10,11} and it could be demonstrated that a considerable proportion of patients were referred to tertiary care centres by their primary or secondary carer.⁹ To fully characterize all levels of medical care, this survey study examined, for the first time, the real life medical attendance situation for urticaria patients in a broad sample of German tertiary referral centres.

The results of this study show that urticaria is a frequent reason for the consultation of tertiary care centres. In contrast to the practice setting where acute spontaneous urticaria preponderates,¹⁰ the most often treated form at the hospital level was reported to be csU. However, other chronic (inducible) forms such as physical urticaria and cholinergic urticaria were also stated to be commonly seen. Although, as yet, only little is known on the prevalence and course of inducible urticaria subtypes, this study found that the gender distribution (equal between genders), age (younger patients) and duration (longer) of these subtypes are different from csU. This is in accordance with the limited previously published data on the natural history of these diseases.^{12–15} Interestingly, the shortest disease duration was reported for childhood csU which was also the least often observed form in the participating centres. In summary, these data indicate that the division of urticaria into different subtypes, as suggested by the guidelines, is important, because these seem to represent entities with a different course and therefore might also require a different management.

According to the current guidelines,² it is recommended to search for underlying causes of csU to enable causal treatment. Notably, all participating centres reported doing so and reported being successful in 45% of attempts, which is considerably higher than what was reported for the practice setting, where a cause can only be found in less than one quarter.¹⁰ Probably, this is due to the fact that the expert centres apply a broader spectrum of

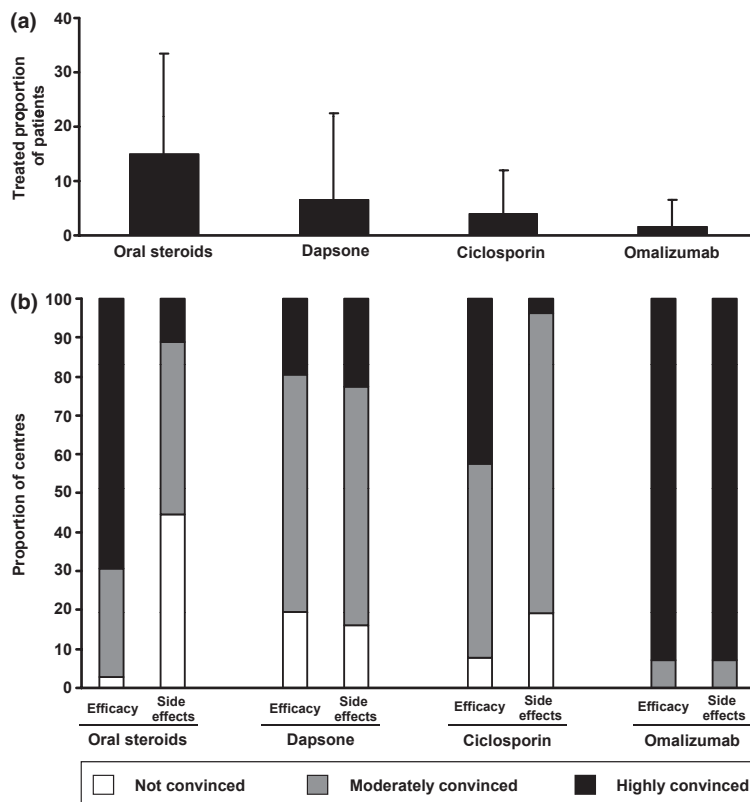


Figure 5 The participating experts were asked for their experience with alternative treatment options in chronic spontaneous urticaria patients, in terms of (a) the mean proportion of patients receiving these therapies and (b) how the centres are convinced by their efficacy. The results are expressed (a) as mean $\pm$ SD and (b) as the proportion of centres that chose the answer options 'not convinced', 'moderately convinced' and 'highly convinced'.

diagnostic measures in more patients as compared to physicians in the practice setting.¹⁰

Interestingly, the most frequent cause was reported to be infection. The role of infections in csU is still a subject of controversial

debates and the available data are inconsistent. This is mirrored by a structured review of Kozel *et al.*¹⁶ summarizing the results of 29 studies with a total number of 6462 unselected urticaria patients. In these studies the number of identified diagnoses varied from 1% to 84% (median: 38%). Furthermore, eight of these studies reported a more than average amount of infections (11–31%) whereas in 11 others infections were designated as the cause in only 0–6% of the patients. Although some authors see increasing evidence that persistent infections are important triggering factors of chronic urticaria,¹⁷ there is a lack of well designed, randomized controlled trials and the exact proportion of patients where infections are truly relevant is still unknown. To enable future research in this field, a clear definition on when an infection can be regarded as relevant is needed. In our study, such a definition was not provided to the participants and the presented data reflect estimations of the participating centres.

The indicated proportion of csU due to intolerance or autoreactivity was similar or lower in this study as compared to previous reports.^{18–21} Intolerance is commonly further subdivided into intolerance to drugs such as salicylic acid and to foods. The relevance of food intolerance as a triggering factor of csU has been demonstrated by two independent studies of our centre showing beneficial effects of a pseudoallergen-free diet.^{18,19} In addition, Di Lorenzo *et al.* also found an improvement of symptoms in many csU patients under food-additive-free diet.²² Further research in

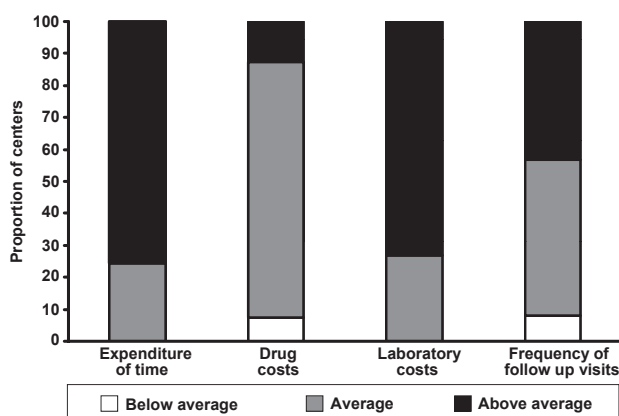


Figure 6 The participating experts were asked for the expenditure of time, drug costs, laboratory costs as well as the frequency of follow-up visits regarding chronic spontaneous urticaria patients. The results are expressed as the mean proportion of centres who chose the respective answer options 'below average', 'average' and 'above average'.

this field is desirable. With regard to our results it is important to note, that the term intolerance was not further defined to the participants.

In the subpopulation of autoreactive csU patients a circulating endogenous factor is present that can induce the symptoms. The commonly used *in vivo* test for autoreactivity is the autologous serum skin test (ASST) which has been shown to elicit positive results in around one-third to almost 50% of patients by most authors.^{20,21} However, the overall range of ASST positive responses in published studies is 4.1–76.5% using different criteria for positivity.²¹ The reported proportion of autoreactive csU in our study is comparably low. Since the centres were not asked how and in how many of their csU patients they actually perform the ASST, possible explanations for the low numbers include differences in the patient selection for the test, in the methodology and in the response interpretation by the participating centres. This implies that there seems to be a need for a broader implementation of the current recommendations for performing the ASST²¹ in daily clinical practice.

Regarding patients with physical and cholinergic urticaria it is important to note that the centres indicated finding an underlying cause in only very few patients, again suggesting that these diseases should be distinguished from csU. For the clinical work it would be of high value to know, which diagnostic measures are most relevant to find underlying causes in urticaria patients. Unfortunately, the design of our study does not allow for an evaluation of different diagnostic measures, but this should be the task of future studies.

The only licensed treatment for csU is the application of H1-antihistamines. Interestingly, the participating experts reported that only one of three patients can be treated sufficiently with these drugs in regular doses, although this number can be increased to two-thirds in case of higher dosing. This is particularly interesting since, up to now, there are only limited data on the efficacy of high-dosed H1-antihistamines and some but not all these studies also point towards a better efficacy of up dosing in some patients.^{23–26} However, the experts indicated that they still see a proportion of around one-third of patients who are resistant to H1-antihistamines. These patients require alternative treatment regimens. As can be expected, the participating hospitals have considerably more experience with these treatment options as it has been reported by practice based physicians.¹⁰

Oral steroids were stated to be applied very infrequently, which is well in accordance with the current guidelines.² These guidelines state that a short course of systemic corticosteroids may be applied to cope exacerbations of csU and do not support a long-term use. Although there are limited data available indicating that a short course of systemic corticosteroids may be helpful to reduce disease severity and duration in patients with acute spontaneous urticaria^{27,28} there are no well-designed studies on their application in csU. Nevertheless, the clinical experience outside of studies shows that they may control the disease in csU patients, including those

resistant to H1-antihistamines. Due to their severe long-term side-effects and because alternative treatment regimens with a better safety profile are available, systemic corticosteroids should, however, be avoided as continuous medication for csU patients if possible.

In a previous study,⁹ many problems regarding medical care of csU patients could be revealed in the practice setting. Notably, these problems can be largely confirmed in the participating tertiary referral centres. The experts reported that the care for csU patients does not only include an expenditure of time and costs that are above average, but also financial restraints and problems at the interface between different health carers. In addition, some patient characteristics, such as a difficult guidance, high expectations and prevalent psychiatric comorbidities that seem to be above average were reported and might also affect care.

This study has strengths and limitations. Major strengths are: first, that it canvassed the opinions of experts from centres of different sizes from all over Germany and therefore represents their large body of experience, second, that it mirrors the real life experience of tertiary referral centres rather than carefully selected data from controlled clinical trials and, third, that it applies an expert-to-expert interview approach thereby assuring a constant comprehension of the survey questions by the different participants. The weaknesses of the study are: first, that the data obtained were based on estimations of the participating experts rather than on the review of medical records and therefore might be subject to a recall bias, and second, that the data cannot be simply generalized to the total csU population (selection bias). Tertiary referral centres see the more severely affected and the more treatment-resistant patients. This is mirrored by the fact that 41.6% of csU patients were reported to suffer from severe urticaria and only 32% to respond to antihistamines at licensed doses, whereas these figures are 20% and 52%, respectively, in the practice setting.¹⁰ To get an insight into the entire situation of csU patient care in real life it is important to consider studies performed in all levels of care.

In conclusion, this study indicates that some urticaria patients, especially those with unknown causes or with an H1-antihistamine-resistant disease, might benefit from a referral to tertiary care centres since the rate of successful identification of causes as well as the experience with alternative treatment options is higher in these centres as compared to the primary or secondary care setting. In addition, this study confirms and extends the results of earlier studies, showing that care for urticaria patient faces problems on various levels. The requirement of much time and resources puts the care for urticaria patients at a particular high risk of suffering from cutbacks in the health care system. However, it is important to note that this study was designed as an explorative project. Therefore, many of the observed results cannot be regarded as definite and should be backed by further research, especially in the following fields:

- 1 Patients with inducible forms of urticaria, such as physical urticaria and cholinergic urticaria as well as children with csU should be better characterized in terms of prevalence, natural history, causes and response to therapy.
- 2 The research on underlying causes of all forms of urticaria needs to be intensified to enable causal or more tailored treatment options.
- 3 There is a big need for randomized, controlled clinical trials on the efficacy of alternative treatment options due to the considerable number of H1-antihistamine-resistant patients.
- 4 The research on urticaria patient needs, stresses and strains, psychiatric comorbidities, impact of the disease as well as external factors that might affect the quality and success of medical care should be expanded.

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