

ORIGINAL ARTICLE

Management of chronic spontaneous urticaria in real life – in accordance with the guidelines? A cross-sectional physician-based survey study

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Abstract

Background Recently, the updated EAACI/GA²LEN/EDF/WAO guidelines for urticaria have been published.

Objective To examine how chronic spontaneous urticaria (csU) patients in Germany are diagnosed and treated, and to compare the outcome to the guideline recommendations.

Methods During this cross-sectional survey study, most dermatologists, paediatricians and 5149 general practitioners in private practice in Germany were asked to participate. All physicians who agreed were requested to complete a standardized questionnaire about their diagnostic and therapeutic management of csU.

Results A total of 776 questionnaires were available for analysis. Most physicians (82%) were attempting to identify underlying causes in their csU patients, but with only limited success. More than 70% reported to check for total serum IgE and to do skin prick testing (not suggested in first line by guideline). In contrast, only 10% applied the autologous serum skin test. The most common first-line treatments were non-sedating antihistamines in standard or higher doses (as recommended). However, many physicians reported still using first generation sedating antihistamines (23%) (not recommended) or systemic steroids (18%). Experience with alternative options was low. Less than one-third of the participants reported to be familiar with the guidelines. Those who did, were found to be more likely to check for underlying causes, to be more experienced with antihistamine up dosing and to be more reluctant to use sedating antihistamines or systemic steroids.

Conclusion The diagnostic and therapeutic management of csU by private practice physicians does not sufficiently comply with the guidelines. Awareness of the guidelines can lead to improved care.

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Conflict of interest

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Introduction

Urticaria is one of the most frequent skin disorders and characterized by recurrent occurring, transient and itchy weals and/or angioedema.¹ It involves a group of heterogeneous diseases with a large variety of possible causes.² The life-time prevalence for any subtype is estimated to be 15–23%.³ This means that almost every fifth person is affected by urticaria over the years. Currently, urticaria is classified into spontaneous urticaria, physical urticaria and other urticaria types.⁴ Chronic spontaneous urticaria (csU) is next to acute spontaneous urticaria by far the most common subtype with a point prevalence of 0.5–1% in the total population.⁵ In contrast to the inducible forms (physical urticaria and other

urticaria types), it is characterized by the spontaneous occurrence of symptoms for more than 6 weeks.⁴ Although the disease is only rarely life threatening, the affected patients suffer from a substantial impairment of their quality of life and performance at work,^{6–8} which is comparable not only to other severe skin disorders⁹ but also serious internal diseases.¹⁰ In addition, csU has been demonstrated to cause high direct and indirect healthcare costs.^{10–12} It often represents a challenging disorder for the patients and their treating physicians.

The updated EAACI/GA²LEN/EDF/WAO guidelines for the definition, classification, diagnosis and management of urticaria have been published recently.^{2,4} The main aim is to identify and

eliminate the underlying cause of csU. As this is frequently not achievable, an effective symptomatic treatment is of major importance for many patients. According to the guidelines,^{2,13} second generation non-sedating antihistamines (nsAHs) in regular doses are recommended as first-line symptomatic therapy. In case of non-response, the dosage can be increased by up to fourfold. If this is not effective, a leukotriene antagonist can be added or the nsAH can be changed to a different compound. Alternative treatment options in the fourth line comprise the addition of H₂-antihistamines or therapy with cyclosporin, dapsone or omalizumab. Systemic steroids are only recommended for a short-term therapy (3–7 days) to cope with exacerbations of the disease.

The guidelines are generated every 4 years by an international panel of specialists from various countries, taking into account all available evidence in the literature and ensuring that their consensus includes European and global regional differences in viewpoint.^{2,4} The current versions^{2,4} were published just after the survey. However, the previous version had been available in the German and English Language for 3 years,^{13,14} and suggested a largely similar diagnostic approach as well as the same first- and second-line treatment.

While the guideline is meant to be employed by ideally all physicians caring for urticaria patients, data on the actual management of patients with csU and on the implementation of the guideline recommendations in real life is scarce. Therefore, we examined the actual clinical practice in Germany in terms of diagnostic and therapeutic proceeding in csU patients in the normal practice setting at a general practitioner (GP), dermatologist or paediatrician shortly before the publication of the updated guidelines in autumn 2009. In addition, we address the question, if an awareness of the guidelines can lead to an improvement of care.

Methods

A nationwide survey on the care for urticaria patients, with a special focus on csU, was conducted in spring 2009 in a sample of German dermatologists, GPs and paediatricians in private practice. In a previous step, most German dermatologists ($n = 2530$), paediatricians ($n = 3531$) as well as 5149 GPs were asked for participation by mail (February to April 2009). These numbers were based on an estimated return rate of 10–20%. In total, 1590 physicians reported their willingness to participate (572 dermatologists, 538 paediatricians, 480 GPs). During the actual survey between February and June 2009, all of the respondents were asked to complete a standardized questionnaire covering several topics: general questions about urticaria (e.g. prevalence, duration, disease activity), questions about the diagnostic and therapeutic management of csU as well as consequences of insufficient symptom control. In addition, questions on how the physicians perceive the patients, self-assessment of the participating physicians and questions concerning the implementation of the current guidelines were addressed. The survey questions were generated by a panel of urticaria experts after a thorough literature review had been performed.

Before the actual onset of the study, the survey has been successfully pretested for comprehensibility and feasibility in a limited number of physicians ($n = 32$), and no changes of the original version were necessary to improve the questionnaire. In total, the survey consisted of 32 questions, mostly involving Likert-scale ratings, quantitative questions, yes/no lists and multiple choice questions (the complete survey can be provided upon request). Person-related data were collected anonymously.

Most of the data analysis was carried out in a descriptive way due to the explorative character of the evaluation with MS-ACCESS, MS-EXCEL and SPSS 17.0. Data that were rated implausible from a medical or biostatistical point of view were excluded from the analysis. However, no questionnaire had to be excluded completely. Comparisons of different groups of participants were carried out using the Mann–Whitney U test or chi-squared test. In this article, we focus on the subset of data on what diagnostic setup is performed in csU patients, how often an underlying cause of the disease can be identified, which treatment options are used and how their efficacy and tolerability is rated. Additional results of the survey (frequency, distribution, duration and severity of urticaria, urticaria patient characteristics such as expectations, psychiatric comorbidity, satisfaction with care as well as economic aspects of care and motivation of the participating physicians) will be published elsewhere.¹⁵

Results

In total, 776 questionnaires were available for analysis from all regions of Germany. A total of 322 (43.0%) of the participants were dermatologists, 215 (28.7%) paediatricians, 206 (27.5%) GPs and 26 (3.5%) belonged to other professional groups, e.g. internal medicine specialists, or provided no information on their training. The mean age of the participants was 50.3 ± 7.9 years, and the majority was men (58.9%). Most physicians (64.4%) stated to practice medicine for < 20 years, 26.7% for < 30 years and 7.7% for more than 30 years. One per cent provided no information on their experience in years. The majority of the participants (72.8%) were working as single practice physicians.

The EAACI/GA²LEN/EDF/WAO guidelines for the definition, classification, diagnosis^{4,14} and management^{2,13} of urticaria is a broad international consensus updated regularly. Approximately one-third of all physicians participating in this survey stated to be familiar with the EAACI/GA²LEN/EDF/WAO guidelines. In dermatologists, the level of knowledge was highest (50.6%) when compared with paediatricians (24.2%) and GPs (12.6%) (Fig. 1). Most of those physicians who declared to be familiar with the guidelines stated that they follow the recommendations in their diagnostic and therapeutic management (dermatologists: 77.9%, paediatricians: 69.2%, GPs: 57.7%).

The current guidelines^{4,14} suggest a panel of basic laboratory tests for all csU patients as well as an extended diagnostic programme for patients with severe and/or long-standing disease to identify underlying causes. The majority (82.0%) of the

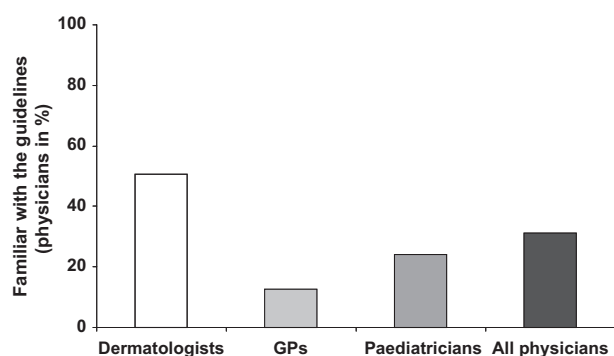


Figure 1 Awareness of the current guidelines. Physicians in the private practice setting were asked if they know the current EAACI/GA²LEN/WAO/EDF-guidelines for the definition, classification and diagnosis and management of urticaria. Results are expressed as percentage of participants who chose the answer option 'yes'.

participants reported that they try to identify underlying causes and, on average, these physicians attempted to do so in about 85% of their patients (dermatologists: 85.1%, paediatricians: 89.2%, GPs: 81.5%). Interestingly, this was reported to be successful in only less than one quarter of attempts (dermatologists: 24.0%, paediatricians: 19.4%, GPs: 24.0%).

The most common diagnostic measures performed were laboratory tests (total serum IgE, differential blood count) and skin prick testing (each performed by $\geq 70\%$ of participants). Less physicians reported to determine C-reactive protein/erythrocyte sedimenta-

tion rate, anti-thyroid antibodies, antinuclear antibodies, serologic analyses and referrals to ear, nose and throat specialists (50–70%) and only 10.1% performed the autologous serum skin test (ASST). Interestingly, diagnostic measures were performed more frequently by those physicians who were familiar with the guidelines when compared with those who were not (Table 1). For example, the ASST was applied significantly more often by physicians who were aware of the guidelines (18.9% vs. 6.0%; $P < 0.001$). However, when asked for the success of their search for underlying causes, no difference could be detected between both groups ($23.8 \pm 20.6\%$ vs. $22.3 \pm 21.6\%$; $P = 0.140$). One reason for this missing difference might be that the frequency and pattern of applied measures was still not ideal in the group who was familiar with the guidelines.

The EAACI/GA²LEN/EDF/WAO guideline for the management of urticaria^{2,13} provides a stepwise treatment algorithm for patients with csU. In accordance with these recommendations, the first choice symptomatic treatment of most physicians (46.0%) in previously untreated patients was reported to be a nsAH in approved dose, followed by a nsAH given at higher doses (30.4%). However, sedating AHs (alone or in combination) and oral steroids were also used by a considerable proportion of respondents (23.0% and 17.9%) as first choice treatment (Fig. 2a). Specifically, sedating antihistamines were the first-line treatment for 19.2% of dermatologists, 25.3% of paediatricians and 27.8% of GPs, whereas systemic steroids were the treatment of first choice for 14.6% of dermatologists, 14.9% of paediatricians and 24.3% of GPs. Interestingly, physicians who were aware of the guidelines

Table 1 Diagnostic procedures performed to identify underlying causes in patients with chronic spontaneous urticaria. Physicians in the private practice setting were asked for the procedures they apply to identify underlying causes in their patients with chronic spontaneous urticaria. All selectable answer options are listed. The results are expressed as percentage of the indicated group of physicians who chose the respective answer option(s)

Procedures	Dermatologists (%)	GPs (%)	Paediatricians (%)	All physicians (%)	Physicians familiar with the guidelines (%)	Physicians not familiar with the guidelines (%)
Total-IgE	81.4	64.6	73.5	74.2	82.7	70.5
Differential blood count	82.3	66.5	68.4	73.8	84.4	69.3
Allergy tests (e.g. prick test)	84.5	51.0	66.0	70.0	83.1	64.5
CRP/ESR	76.7	62.1	57.2	66.9	77.0	62.2
Thyroid hormones and autoantibodies	65.2	57.8	40.9	55.4	69.1	49.2
Autoimmune diagnostics (e.g. ANA)	68.3	43.7	46.0	53.7	68.7	46.9
Serological analyses	67.7	40.3	44.2	52.4	63.4	47.5
Consultation of an ENT-specialist	77.6	36.9	24.2	50.3	66.3	43.1
Consultation of a dentist	77.3	26.2	15.3	44.6	63.4	36.1
Pseudoallergen low diet	69.3	21.8	26.0	43.0	61.7	34.0
Test for <i>Helicobacter</i>	64.6	29.1	20.0	41.5	60.1	33.0
C1-INH	59.3	16.5	38.6	40.7	56.0	33.6
Microbiological examinations	61.8	19.9	29.3	39.9	57.2	32.0
Imaging (e.g. ultrasound)	28.3	23.3	9.8	20.9	27.6	17.6
Others	28.9	19.4	9.3	20.9	22.6	20.3
Autologous serum skin test	17.7	4.4	5.1	10.1	18.9	6.0

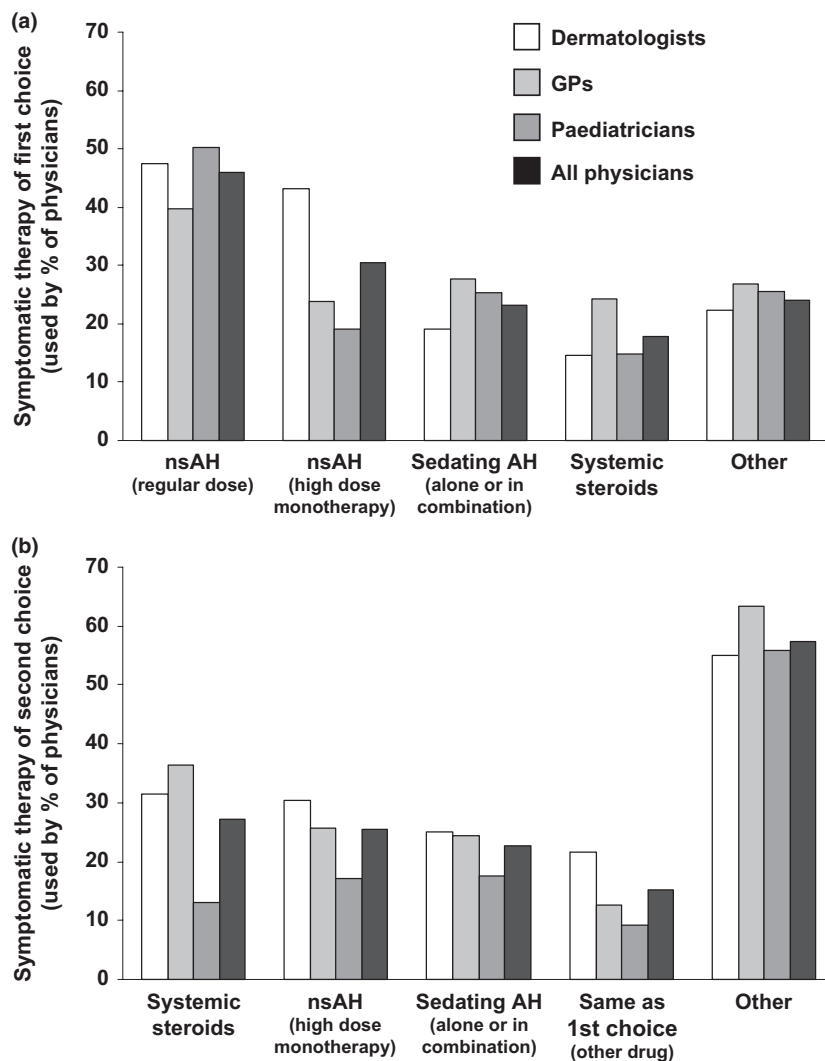


Figure 2 Symptomatic therapy of first and second choice in patients with chronic spontaneous urticaria. Physicians in the private practice setting were asked for (a) their symptomatic therapy of first choice in previously untreated patients and (b) which treatment they recommend to those patients who do not respond sufficiently to their recommended first-line therapy. Results are expressed as percentage of participants who chose the respective answer.

were significantly less likely to report an application of sedating antihistamines as first-line treatment when compared with those who were not ($P < 0.05$). No differences were found with regard to the use of systemic steroids ($P = 0.807$).

In around one-third of patients, the first applied therapy was reported to not be successful (dermatologists: 32.9%, paediatricians: 33.5%, GPs: 32.7). In this case, the physicians most frequently used oral steroids (27.2%), high dosage nsAHs (25.4%), sedating AHs (alone or in combination) (22.6%) or treatment options of first choice, but with a different compound (15.3%) (Fig. 2b). Again, physicians who were aware of the guidelines were significantly less likely to use sedating antihistamines when compared with those who were not ($P < 0.05$). In addition, physicians who were aware of the guidelines were significantly less likely to use systemic steroids ($P < 0.05$).

Asked explicitly for the efficacy of nsAHs, the participating physicians reported that only around half of the patients (52.3%)

can be sufficiently treated with standard doses, which is the only currently approved treatment option for csU. Interestingly, this number was stated to be higher (63.2%) when asked for nsAH-treatment with increased doses (nsAH up dosing). The proportion of dermatologists who reported to have experience with nsAH up dosing was highest (92.5%; paediatricians: 47.9%; GPs: 69.9%) and this group even reported that only 45.3% of the patients can be sufficiently treated by regularly dosed nsAHs, whereas, this is true for 64.9% in case of applying high dosed nsAHs (Fig. 3a). Importantly, physicians who were familiar with the guidelines were more likely to have experience with up dosed nsAHs (86.0% vs. 67.2%; $P < 0.05$).

No adverse effects were reported to be experienced by 79.2% of patients receiving regular dosed nsAHs and by 73.3% treated with high-dosed nsAHs indicating that an up dosing does not seem to go along with a marked increase of the frequency of adverse effects (Fig. 3b). In case of a combination of nsAHs and H_2 -blockers,

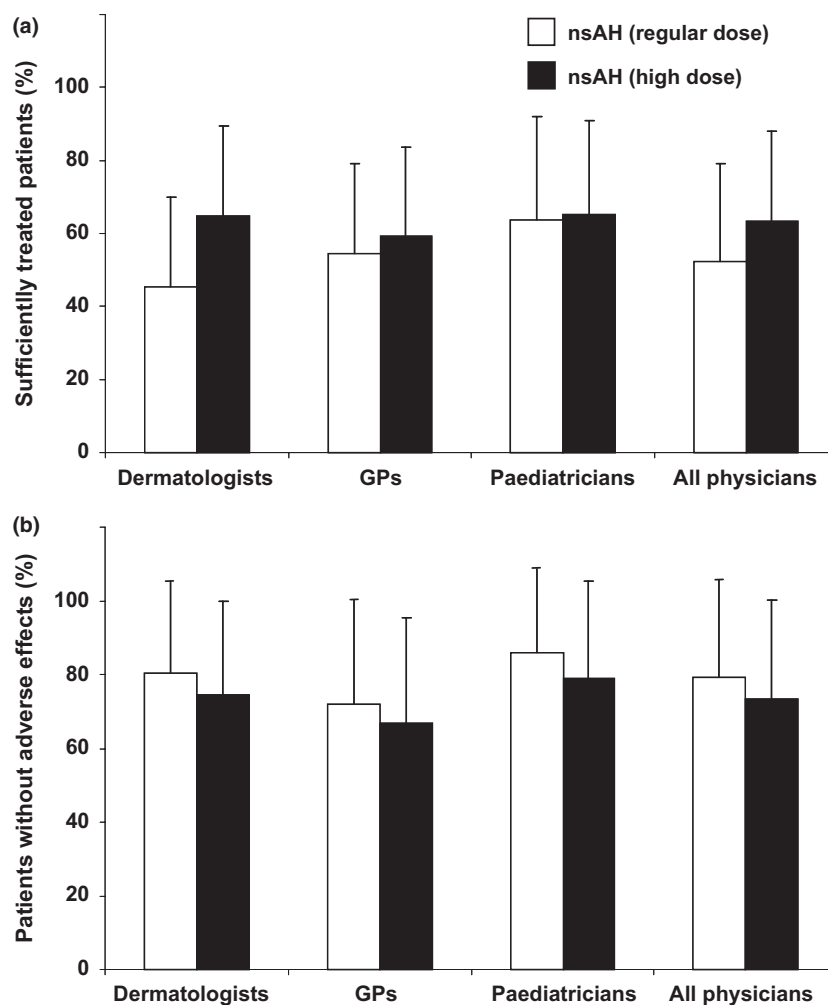


Figure 3 Efficacy (a) and adverse effects (b) of standard and higher than standard dosed non-sedating antihistamines (nsAH) in patients with chronic spontaneous urticaria. Physicians in the private practice setting were asked for (a) the percentage of patients who can be sufficiently treated by standard and higher than standard dosed nsAH and (b) the proportion of patients who do not experience unwanted effects as individually estimated by the participants. Results are expressed as mean $\pm$ SDs.

nsAHs and leukotriene inhibitors as well as a combination of all three, the percentage of sufficiently treated patients was reported to be 58.7%, 61.9% and 67.4% respectively.

Alternative treatment options are of major importance for those csU patients who do not respond sufficiently to standard or higher than standard dosed nsAHs. Dermatologists were found to be more experienced with alternative treatment options (e.g. dapson: 32.0%, other immunosuppressants: 26.1%), when compared with paediatricians (dapson: 1.4%, other immunosuppressants: 3.3%) or GPs (dapson: 6.3%, other immunosuppressants: 12.6%) (Fig. 4). Experience with omalizumab, which has been included for the first time in the updated guidelines (published after the survey) as an alternative therapy, was very low. In total, only 28 of all participants (3.6%) reported to have experience with this drug.

Discussion

This is, to our knowledge, the first study that examined the actual treatment of patients suffering from csU in the real life practice

setting in Germany with regard to the at that time published guidelines^{13,14} and recently updated guidelines.^{2,4}

The guidelines suggest a diagnostic programme for patients with severe and/or long-standing csU aimed at the identification of underlying causes.^{4,14} Interestingly, most of the participating physicians reported to perform various diagnostic measures to do so, but the pattern was only partly in accordance with what is known about the actual frequency of the different causes. For example, skin prick tests and serum IgE measurements were done more frequently than other more important diagnostic measures such as the search for an infectious focus or autoreactivity, although classical type-I allergies are only a rare cause of csU.¹⁶ In contrast, autoreactive csU is one of the most frequent subtypes of the disease,¹⁷ and only approximately 10% of participants seem to screen for it using the ASST. Interestingly, those physicians who were familiar with the guidelines were significantly more likely to perform the ASST. However, even in this group, the test is still only performed by one of five physicians. The reasons for this might be (i) that the test is time consuming and

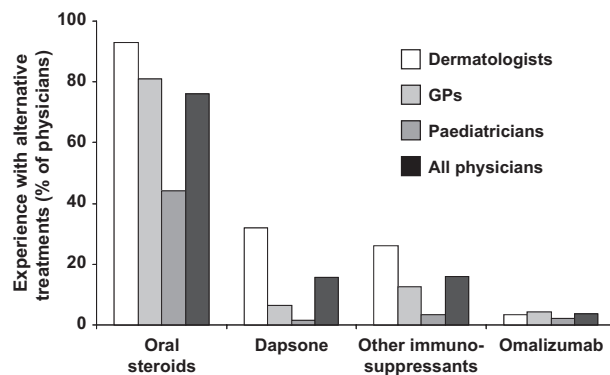


Figure 4 Experience with alternative treatment options for chronic spontaneous urticaria. Physicians in the private practice setting were asked if they have experience with the following alternative treatment options in patients with chronic spontaneous urticaria: dapsone, oral steroids, immunosuppressants (e.g. cyclosporin), omalizumab, and others. 'Others' was chosen by $n = 33$ dermatologists (10.2%), $n = 10$ paediatricians (4.7%) and $n = 6$ GPs (2.9%) (data not shown). In this category the participants mentioned treatment with autologous blood injections, homoeopathy, microbiologic therapy and bioresonance therapy, among others. Results are expressed as the percentage of participants who chose the respective treatment option.

has to be performed with utmost care because infections might be transmitted if, by mistake, patients were injected with someone else's serum,⁴ and (ii) that it was mentioned, but not particularly recommended in the at that time published version of the guidelines.¹⁴

Notably, the participating physicians reported that they are able to identify an underlying cause of csU in only less than one quarter of attempts. This indicates that the symptomatic treatment remains the mainstay of therapy for the majority of patients in the practice setting. A limitation of this result might be that no clear definition was provided to the participants on what should be regarded as a cause of the disease. For example, some physicians might have considered the detection of a positive ASST as a successful identification of a cause, whereas others might have not. One reason for not providing a clear definition to the participants was the fact that there is still no consensus on what findings under which circumstances can be regarded as a cause of urticaria. Another major problem is that the determination of the true relevance of a suspected cause is frequently not possible in the real life practice setting. Reasons for this include the fact that patients tend to not return for a follow-up visit in case their disorder has been successfully cured in contrast to those patients who still suffer from symptoms.

Interestingly, the physicians who were familiar with the current guidelines did not seem to be more successful in finding underlying causes in their csU patients. The reason for this is not entirely

clear. One possible explanation is that the frequency as well as the pattern of performed measures was still not ideal in this group. The hypothesis that a more intensive diagnostic programme might lead to a higher detection rate is supported by another survey study that has been performed in the tertiary care setting where a higher frequency and a broader spectrum of applied measures went along with a higher proportion of patients with successfully identified causes.¹⁸ However, there are also other works available who did not find a relationship between the number of identified diagnoses and the number of performed laboratory tests. More research on this important issue is urgently needed to clarify the true value of diagnostic measures in csU.¹⁹

In the guidelines, the recommended first-line symptomatic treatment is regular-dosed nsAHs, followed by nsAHs in high dose.^{2,13} While nsAHs were actually being used by the majority of the physicians as the first-line treatment, around one-third of physicians began therapy with increased doses of nsAHs. Sedating AHs and systemic steroids, which can be considered obsolete, were still used by a meaningful number of physicians. Sedating antihistamines are by mistake generally regarded as safe by many laypersons and healthcare professionals, because of their long-standing use. However, they have been shown to reduce rapid eye movement-sleep, impair learning and reduce work efficiency,²⁰ and they are implicated in traffic accidents, deaths as a result of accidental or intentional overdosing and exhibit cardiotoxicity in overdose.²⁰ Interestingly, the group of physicians who stated to be familiar with the guidelines were less likely to use sedating antihistamines and systemic steroids as a first- and/or second-line treatment, indicating that guideline recommendations may improve the quality of care.

The concept of increasing the dose of nsAHs in csU patients who do not respond sufficiently to regular doses, is one of the central treatment recommendation of the guidelines.^{2,13} Both clinical experience and clinical studies support this approach.^{21–23} However, the evidence is still limited. Therefore, it is interesting to note that the participants of this study reported that high dosing of nsAHs is effective in a higher percentage of patients when compared with regular doses. On the other hand, still around one-third of patients were reported to be antihistamine resistant regardless of which dose is used. This is well in accordance with previous publications applying responder analyses.^{16,23} Of course the results on the efficacy of antihistamines are just a rough and subjective estimate of the participating physicians. Therefore, the response rates might not be directly comparable to those obtained by randomized, controlled, pharmacological trials and a bias towards a more general perception rather than a clear reflection of the actual success of their treatment regimen cannot be excluded. However, the results mirror the doctor's experience in their real life practice setting and this may also be regarded as a strength of this survey, because it is well established that results gained from a highly selected study population are probable to also not fully represent all patients.

In case of insufficient symptom control with nsAHs, the updated guidelines² suggest the addition of a leukotriene antagonist or a change of the nsAH followed by alternative treatment regimens. Interestingly, only few experience existed with alternative treatment options and only the subgroup of dermatologists had meaningful experience with dapsone and immunosuppressants, e.g. cyclosporin. One might speculate that these treatment options are too complicated and maybe also too expensive in the practice setting, because they require intensive monitoring. Another reason for the limited application might be the fact that some of these options are 'off-label' and that an 'off-label use' in the practice setting frequently results in a recourse proceeding for the practitioners in Germany.

Interestingly, the alternative treatment options did not convince the majority of those participants having experience with these drugs. This is in line with the current literature, showing only limited benefit of dapsone therapy²⁴ and providing only limited or anecdotal supportive evidence for immunosuppressants.²⁵ Only for cyclosporin, there is considerable evidence available supporting its efficacy in csU.^{26,27} In summary, there seems to be a lack of successful and safe long-term treatment options for many csU patients. This implies a need for new and effective therapies. The updated guidelines² refer to omalizumab (anti-IgE) as a new alternative therapeutic option on the same recommendation level as H₂-antihistamines, dapsone or cyclosporin. We and others have previously demonstrated that omalizumab is effective in patients with csU^{28–30} as well as in other urticaria subtypes.³¹ However, in the real-life practice setting, the experience with omalizumab is still very low. Further research in form of double-blind placebo-controlled studies is desirable to confirm the efficacy and safety of this new treatment option.

In physician survey studies carried out on a voluntarily basis, a selection bias is always likely to occur. Among others, it can be assumed that the 'better' and 'more dedicated' physicians are more probable to take part in such studies. This may affect the generalizability of our results to the general population of dermatologists, paediatricians and GPs, and has to be taken into account when interpreting the data. However, we strongly believe that this limitation is less likely to essentially change the character of our results.

In conclusion, the real-life diagnostic and therapeutic management of urticaria patients in the practice setting is only partly in accordance with the guidelines, and their general level of implementation is low. The results of this study suggest that awareness of the guidelines may lead to an improvement of quality of care. Therefore, more efforts to enhance the guideline implementation are necessary to optimize the diagnostic and therapeutic management of csU patients. This is likely to lead to a better symptom control and quality of life of the affected patients as well as to a reduction of inappropriate treatment approaches that may cause avoidable side effects, e.g. the long-term use of systemic steroids and sedating antihistamines.

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