

ORIGINAL PAPER/PRACA ORYGINALNA

## Diagnostic and treatment trends in chronic urticaria. Retrospective and prospective analysis of patients from the Department of Dermatology, Poznan University of Medical Science

Trendy w diagnostyce i leczeniu pokrzywki przewlekłej.  
Retrospektywna i prospektywna analiza pacjentów  
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### ABSTRACT

**Introduction:** Confirmation of the cause of chronic urticaria (CU) seems a great challenge for specialists. The aim of pharmacological treatment is to reduce the effect of mediators released from mast cells on target organs and to reduce symptoms.

**Aim:** To analyse the diagnostic and treatment trends in CU.

**Material and methods:** The study was divided into two parts. Retrospective (R) analysis included 441 CU patients at the age of 15 or older hospitalized during 10 years. Information from history of the disease was entered in a specially designed form. For the prospective (P) analysis 78 patients were chosen out of 441 subjects previously qualified for retrospective analysis. Patients from the P part were divided into subgroups I and II in terms of persistence of symptoms.

**Results:** The most frequently performed tests were the aspirin test (79.6%), autologous serum skin test (ASST) (79.4%) and provocation by pressure (70.7%). Significant differences concerning the type of urticaria, in which an increased C-reactive protein level was detected the most frequently, were found in spontaneous, autoimmune and aspirin-induced urticaria. There was observed a significant increase in the frequency of the determination of thyroid hormones and anti-thyroid antibodies over the years. Most frequently the patients received second-generation antihistamines (63% R; 88.4% P). There was reported less usage of first generation of antihistamines over the years (from 27.9% to 3.7%). The cause of symptom relief in subgroup II was mainly pharmacotherapy (37.1%).

**Conclusions:** The obtained results agreed with most reports concerning diagnosis and treatment of CU.

### KEY WORDS

chronic urticaria, antihistamines, autologous serum skin test, angioedema.

## STRESZCZENIE

**Wprowadzenie:** Potwierdzenie przyczyny pokrzywki przewlekłej (CU) stanowi spore wyzwanie dla lekarza specjalisty. Celem leczenia farmakologicznego jest zmniejszenie wpływu mediatorów uwalnianych z komórek tucznych na narządy docelowe i zmniejszenie objawów.

**Cel:** Analiza trendów diagnostycznych i leczniczych w CU.

**Materiał i metody:** Badanie podzielono na dwie części. Analiza retrospektywna (R) objęła 441 pacjentów z CU w wieku 15 lat lub starszych, hospitalizowanych w ciągu 10 lat. Informacje z historii choroby umieszczono w specjalnie w tym celu zaprojektowanym formularzu. Do analizy prospektywnej (P) wybrano 78 pacjentów spośród 441 osób wcześniej zakwalifikowanych do analizy retrospektywnej. Pacjentów z części P podzielono na podgrupy I i II na podstawie utrzymywania się objawów.

**Wyniki:** Najczęściej wykonywanym badaniem była próba aspirynowa (79,6%), test skórny z autologiczną surowicą – ASST (79,4%) i prowokacja uciskiem (70,7%). Istotne różnice dotyczące odmiany pokrzywki, w przypadku której najczęściej wykrywano podwyższony poziom białka C-reaktywnego, występowały w pokrzywce spontanicznej, autoimmunologicznej oraz aspirynowej. Na przestrzeni lat zaobserwowano znaczny wzrost częstości oznaczania hormonów tarczycy i przeciwciał przeciwtarczycowych. Najczęściej odnotowywano przyjmowanie przez chorych leków przeciwhistaminowych II generacji (63% R; 88,4% P). Zaobserwowano mniejsze użycie leków przeciwhistaminowych I generacji na przestrzeni lat (z 27,9% do 3,7%). Przyczyną ustąpienia objawów w podgrupie II była głównie farmakoterapia (37,1%).

**Wnioski:** Uzyskane wyniki pokrywają się z większością doniesień dotyczących diagnostyki i leczenia CU.

## SŁOWA KLUCZOWE

pokrzywka przewlekła, leki przeciwhistaminowe, test skórny z autologiczną surowicą, obrzęk naczynioruchowy.

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## INTRODUCTION

Urticaria is a disease with a complex pathomechanism that is characterized by the occurrence of wheals, oedema or both at the same time. Skin changes are accompanied by pruritus and/or sometimes burning sensation. Different types of urticaria have a very wide range of clinical manifestations and in one patient more than one of its types may co-exist.

Confirmation of the cause of chronic urticaria (CU) seems a great challenge for specialists. Before selecting tests, all regional and dietary diversity as well as the incidence of infection should be taken into account. According to EAACI/GA<sup>2</sup>LEN/EDF/WAO guidelines from 2017 [1] and Polish recommendations [2], the first stage of diagnosis is a very detailed interview with the patient. The next step is physical examination, which should include challenge tests selected in accordance with the interview.

Management of urticaria includes: elimination or avoidance of the causative factor, pharmacological symptomatic treatment, reducing the release of mediators

from mast cells and/or limiting their action on target organs, inducing tolerance. The aim of pharmacological treatment is to reduce the effect of mediators released from mast cells on target organs and reduction of symptoms.

## AIM

The aim of the study was to analyse the diagnostic and treatment trends in chronic urticaria.

## MATERIAL AND METHODS

The study was divided into two parts – the retrospective one (R) and the prospective one (P). Patients from the P part were divided into subgroups I and II in terms of persistence of symptoms.

Retrospective analysis included 441 CU patients at the age of 15 or older hospitalized in the Department of Dermatology, Poznan University of Medical Sciences during 10 years. The study analysed history of the disease of all patients and then anonymized information was entered

in a specially designed form. For the prospective analysis 78 patients were chosen out of 441 subjects previously qualified for retrospective analysis, suffering from chronic aspirin-exacerbated disease, spontaneous, autoimmune and induced urticaria.

### STATISTICAL ANALYSIS

Statistical analysis was carried out in the IBM SPSS program (ver. 23).

### RESULTS

The analysis summarizes all the diagnostic tests performed in patients with chronic urticaria. The most frequently performed tests were the aspirin test (79.6%),

autologous serum skin test (ASST), (79.4%), as well as provocation by pressure (70.7%). Total IgE in blood serum (2.7%) and antinuclear antibodies (5.9%) were measured least frequently. There was no food provocation performed in any of the patients. The most frequent deviations appeared in the autologous serum skin test (21.8% positive results), as well as in the aspirin test (14.5% positive tests) (Figures 1, 2). Among other abnormalities found in the patients, parasitic infection was predominantly present (20.6%), as well as increased erythrocyte sedimentation rate (ESR) (15.4%).

Further analysis concerned the type of urticaria, in which increased C-reactive protein (CRP) level was detected the most frequently. Significant differences were found in spontaneous, autoimmune and aspirin-induced urticaria (Figure 3).

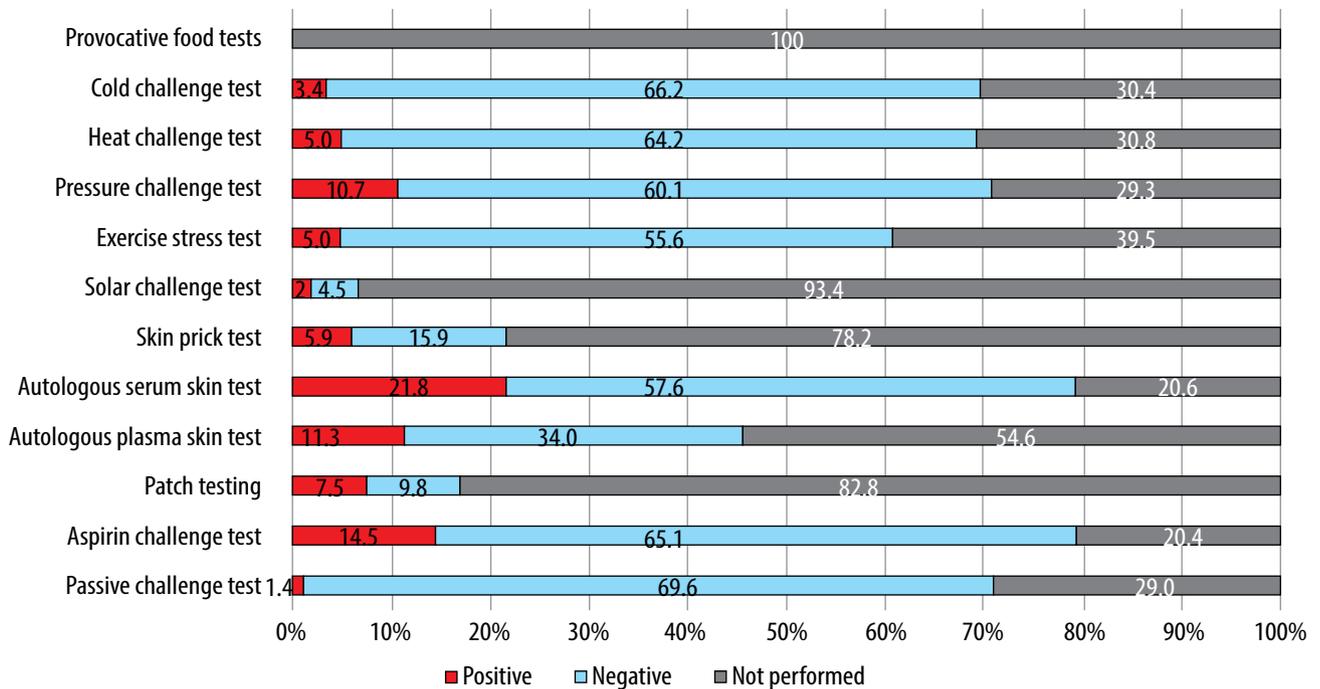


FIGURE 1. Performed diagnostic tests – part I

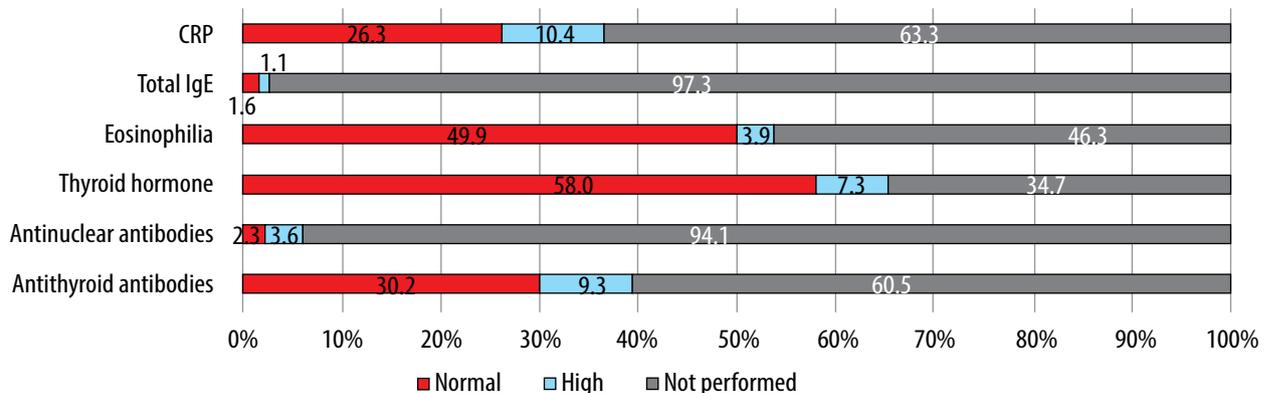
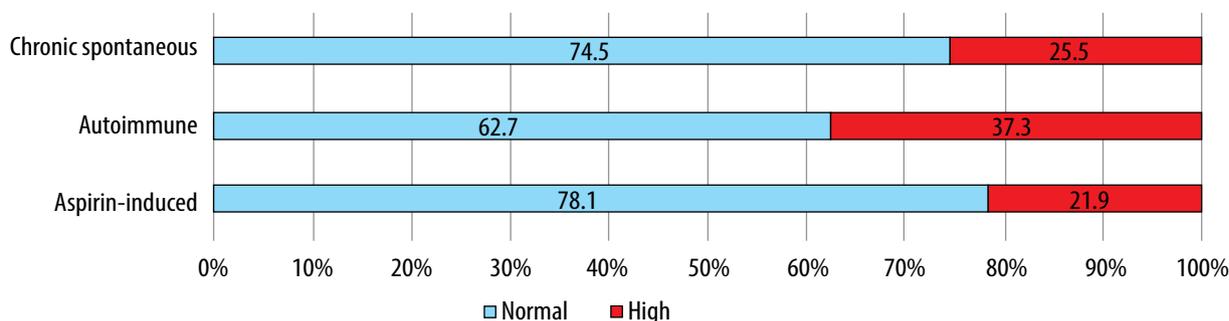
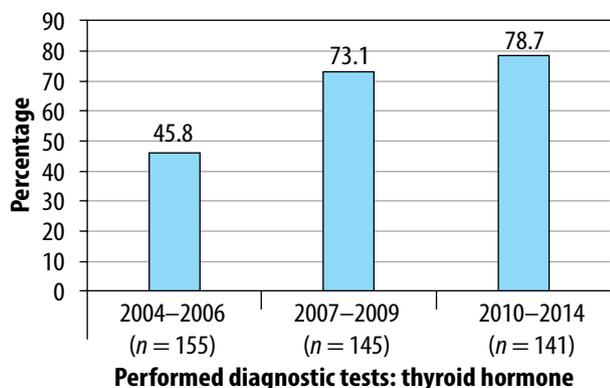


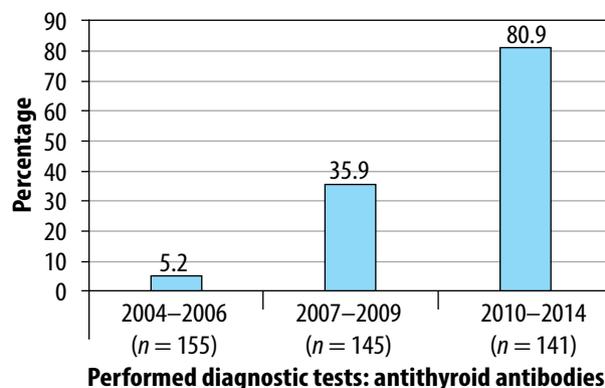
FIGURE 2. Performed diagnostic tests – part II



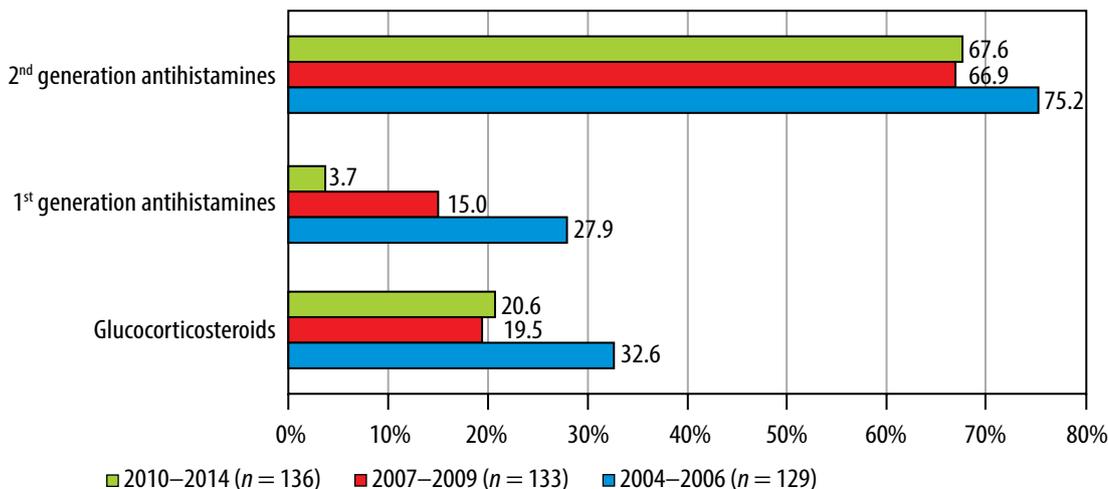
**FIGURE 3.** Elevated levels of CRP in accordance with different types of urticaria



**FIGURE 4.** Diagnostic tests in particular years of admission: thyroid hormone



**FIGURE 5.** Diagnostic tests in particular years of admission: antithyroid antibodies



**FIGURE 6.** Percentage of selected drug groups in therapy in particular years

Moreover, it was assessed how the diagnostic profile of thyroid hormones and anti-thyroid antibodies changed in particular years of admission to the clinic: 2004–2006, 2007–2009, 2010–2014. The number of patients admitted in these intervals slightly differed. However, in both cases, a significant increase in the frequency of their determination was observed, especially in the presence and level of anti-thyroid antibodies (Figures 4, 5).

Further analysis concerned the medications which patients were receiving for urticaria just before hospital-

ization. In part R most frequently the patients received second-generation antihistamines (63%), followed by glucocorticosteroids (22%) and first-generation antihistamines (13.8%). However, 19.5% had not taken any medications before hospitalization. The vast majority of 43 people from subgroup I in the P part were receiving medications for urticaria (88.4%). The most common were second-generation antihistamines (86%), then glucocorticosteroids (23.3%) and first-generation antihistamines (14%). It is worth noting that in both parts of the

analysis no use of omalizumab, thyroxine, sulfasalazine or phototherapy was reported. Among other therapeutic options, it is worth mentioning a significant percentage of respondents using an aspirin diet, and additionally, in part R psychotropic drugs.

In R there was also analysed the percentage of selected drug groups in therapy in particular years, of which the beginning was determined on the basis of new guidelines for the treatment of CU (Figure 6). The number of hospitalized patients in those years did not differ significantly, but it is very important that first-generation antihistamines were used much less frequently (from 27.9% to 3.7%).

Out of 43 patients in subgroup I, slightly more than half noticed an improvement in their health (51.2%). In this subgroup, 90.7% of patients did not have new symptoms.

The causes of symptom relief in subgroup II in P were pharmacotherapy (37.1%), spontaneous remission (28.6%) and elimination diet (25.7%).

## DISCUSSION

As mentioned earlier, the search for the causative agent in CU is a difficult challenge for a specialist doctor. The guidelines strongly suggest that detailed and costly diagnostics should not be routinely performed. That is why an interview with the patient is so important. Only a few authors have taken up the topic of diagnostic tests in their publications. Interestingly, Zuberbier *et al.* [3] proved in their double-blind placebo-controlled food challenge analysis (DBPCFC) that IgE-dependent food allergy did not cause urticaria symptoms in any of their patients. In 18.2% of respondents they obtained a positive reaction, but manifested only as oral allergy syndrome (OAS), limited itching or shortness of breath. None experienced wheals.

Many authors emphasize the role of anti-thyroid antibodies and thyroid hormones in CU [4–12]. The results did not confirm this thesis, but many publications indicate that the contribution of these indicators may be significant in patients with CU. Fatani *et al.* [13] found no significant correlation between the occurrence of abnormalities in these indicators and the occurrence of CU. However, other authors have reported a significant relationship between these indicators and the presence of urticaria in comparison with the control group [7, 10, 12, 14–16]. They all found significantly increased levels of antibodies and hormones in patients, Turktas *et al.* [15] in 21.3%, and Verneuil *et al.* [12] in 26.7%. Significant results were also obtained by Pan *et al.* [8] in their meta-analysis including 20 publications, in which they found that in patients with CU anti-thyroid antibodies are more

frequently detected than in the control group (primarily anti-TPO). The other authors did not analyse the above aspect in such detail. Ferrer [17] only reported that the determination of the level of anti-thyroid antibodies and thyroid hormones was performed with high frequency (45.2% and 62.1%), while Gaig *et al.* [18] did not include thyroid tests at all in the diagnosis.

As mentioned earlier, the most frequently performed test and the one with the most abnormalities was ASST. The autoimmune basis in chronic spontaneous urticaria is searched for and detected (it is believed that even in half of the cases) very commonly [19]. Zhong *et al.* [20] obtained a positive result in the autologous serum test in 66.9% of patients with chronic spontaneous urticaria (CSU) who underwent the test. Moreover, the Urticaria Activity Score (UAS) and Dermatology Life Quality Index (DLQI) results in these patients were significantly higher than in those with a negative ASST result. The duration of the wheals was also longer and the incidence of angioedema was higher. Ferrer, on the other hand, reported that ASST was performed in only 1.2% of patients with CU [17].

Some of the most recent studies pay attention to certain parameters of inflammation. There are sought biomarkers in the pathogenesis of chronic urticaria, e.g. elevated levels of erythrocyte sedimentation rate (ESR), anti-streptolysin O (ASO), CRP, D-dimers or eosinophilia. Increasingly, these parameters are the target of diagnostics. Brazilian authors obtained elevated ESR in 8.7% and eosinophilia in 7.7% [21]. In a study conducted on the Arab population, increased ESR was noted in 63% of all study participants, while only mean values were given for eosinophilia and CRP [13]. Both values were within the normal range (2.25% for eosinophilia and 1.22 mg/l for CRP). A much higher levels of these indicators has been observed in patients with acute urticaria. Mansi *et al.* [22] noted an increased value of peripheral eosinophilia > 5% only in 5% of the study group.

In the case of parasitic infections Silveiras *et al.* [21] found the presence of parasites in faeces only in 5.7% of all participants. In the Spanish population, in two different analyses, faeces were examined in 38.7% and 10.7% [17, 18]. However, it is not known how many of them obtained positive results. In this analysis, the determination of total IgE in the blood serum was very rarely reported (2.7%), while Ferrer [17] estimated this frequency as 67.3%, and Zuberbier *et al.* as 66.7% [3]. In none of the available analyses was information about performing particular challenge tests found. Very generally, the Spanish publication defined the frequency of physical tests at 22.2% [17]. Nor was the aspirin test mentioned in any of the publications. However, the results regarding the skin biopsy are very divergent. Two independent Spanish analyses reported values of 11.8% and only 0.8% [17, 18].

When treating urticaria, it is very important to define its cause precisely. Unfortunately, this is not always possible. Therapy of different types of urticaria is equal and mostly antihistamines are used. According to the latest guidelines, the use of the first generation of these drugs is not recommended due to their negative effect on the CNS.

The collected epidemiological data correspond to a great extent with the obtained results. Many authors confirmed the use of antihistamines in CU. Valero *et al.* [23] reported that 93.4% of patients in the Spanish clinic used antihistamines. However, they did not specify the division into generations. In another study conducted on the Spanish adult population frequent use of glucocorticosteroids was noted (32.9%) [18]. In the publication of Fatani *et al.* [13] it was noted that the use of the first generation was 15%, the second-generation 24.4%, and the glucocorticosteroids (GCS) 30.3%. Moreover, patients who did not notice any improvement were given H2-blockers. Jankowska-Konsur *et al.* [24] reported that in the CSU group antihistamines were used more often in higher doses than the registered ones. Very interesting reports were presented by Brazilian and Portuguese researchers, who reported that 60% of patients chronically used antihistamines, of whom 94% were taking hydroxyzine, 27% cetirizine, and 15% fexofenadine [25]. None of the publications analysed the remaining therapeutic options and only Gaig *et al.* [18] reported the use of diet and antidepressants in therapy (9.3% each). Many reports emphasize the positive role of omalizumab in CSU patients, especially the dose of 300 mg and higher, which turned out to be more effective than 150 mg or lower [26–28].

In the case of subgroup II in P, the reasons for the withdrawal of changes were also analysed. It was found that in most cases it was treatment (37.1%), followed by spontaneous remission (28.6%) and elimination diet (25.7%). It is also worth noting that the eradication of parasites or elimination of chronic inflammation (11.4%) caused the remission. Therefore, despite the lack of recommendations in the guidelines for the diagnosis of parasitic infections, detecting this potential causative factor, postulated by many authors, turns out to be important. Many reports showed a significant role of stress and mental disorders in the exacerbation or induction of CU symptoms, which was also confirmed in this study [29–32]. Psychiatric treatment and avoiding stress resulted in remission in 8.6% of patients.

## CONCLUSIONS

The obtained results agreed with most world reports concerning diagnosis and treatment of CU. This complex

and important issue deserves to be precisely and thoroughly analysed.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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