A European survey of management approaches in chronic urticaria in children: EAACI pediatric urticaria taskforce

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S.T and TA.L. initially conceptualized this study. All authors contributed to the data collection, data analysis, data interpretation, and preparation of the report. S.T., MK.C., S.A., & TA.L. assumed the main responsibility for the manuscript writing. B.B provided methodological support. B.B, M.AL., C.C., C.F., SR. J., GN.K, S.L.,CG.M, G.P, H.P., K.R., LA.VdP contributed in conceptualizing the study and critically reviewed draft versions. All authors contributed to (and agreed upon) the final version.

Abstract

Background: Although well described in adults, there are scarce and heterogeneous data on the diagnosis and management of chronic urticaria (CU) in children (0-18 years) throughout Europe. Our aim was to explore country differences and identify the extent to which the EAACI/GA²LEN/EDF/WAO guideline recommendations for pediatric urticaria are implemented.

Methods: The EAACI Taskforce for pediatric CU disseminated an online clinical survey among EAACI pediatric section members. Members were asked to answer 35 multiple choice questions on current practices in their respective centres.

Results: The survey was sent to 2,773 physicians of whom 358 (13.8%) responded, mainly pediatric allergists (80%) and pediatricians (49.7%), working in 69 countries. For diagnosis, Southern European countries used significantly more routine tests (e.g., autoimmune testing, allergological tests, and parasitic investigation) than Northern European countries. Most respondents (60.3%) used a 2nd generation antihistamine as first- line treatment of whom 64.8% up dosed as a second- line. Omalizumab, was used as a second line treatment by 1.7% and third-line by 20.7% of respondents. Most clinicians (65%) follow EAACI/WAO/GA2LEN/EDF guidelines when diagnosing CU, and only 7.3% follow no specific guidelines. Some clinicians prefer to follow national guidelines (18.4%, mainly Northern European) or the AAAAI practice parameter (1.7%).

Conclusions: Even though most members of the Pediatric Section of EAACI are familiar with the EAACI/WAO/GA2LEN/EDF guidelines, a significant number do not follow them. Also, the large variation in diagnosis and treatment strengthens the need to re-evaluate, update and standardize guidelines on the diagnosis and management of CU in children.

Key words: child; chronic urticaria; omalizumab; urticaria diagnosis; urticaria treatment.

Key message: This survey was undertaken in order to determine how pediatric urticaria patients are being managed by EAACI pediatric section members. The respondents included pediatric allergists, immunologists, dermatologists, and pediatricians. It adds background clarity as to how children all over Europe are being treated for this debilitating disease.

Responses to the questionnaire showed that the majority of patients are treated with second-generation antihistamines, which are updosed after 2-4 weeks, in keeping with the current guidelines, with cetirizine being the antihistamine of choice in children under 6 years of age. Omalizumab was used by a fifth of respondents as a third-line treatment, as recommended by the EAACI guideline, in addition to a small percentage using omalizumab as a second-line treatment.

The results of this study demonstrate that while most clinicians are now managing their patients according to EAACI guidelines, there is scope for improvement and that further re-evaluation, updating, and standardisation of protocols will be helpful in this. The findings of the survey should have a positive impact on clinicians' confidence in using the EAACI algorithm in children. Clinicians are updosing antihistamines safely as per the guidelines and using omalizumab which has proved to be a safe treatment in children with no reports of anaphylaxis. The main adverse effect was local injection site reaction. The authors hope to reinforce to readers that the algorithm is not only suitable in children but provides an optimal approach to treatment of pediatric urticaria.

Introduction

Chronic urticaria (CU), both spontaneous and inducible, although not life-threatening, is a burden on both the physical and socio-psycho-economic state of the patients.[1, 2] Comorbidities, such as anxiety, depression, and sleep disorders limit daily life, work/school and sports activities and interfere with life within the family and in society.[3-6] Furthermore, its management can be complex and challenging. The EAACI/GA²LEN/EDF/WAO [7] guideline provides clinical recommendations for the definition, classification, diagnosis and management of urticaria. However, because CU is less common and less studied in children than adults, treatment options in the guideline are based on adult data which have been extrapolated for children.

To investigate CU in children in more detail, an EAACI Taskforce was created to investigate current clinical practice in the diagnosis and management of childhood CU, mapping activity, understanding country differences and challenges, and identifying the

extent to which the EAACI/GA²LEN/EDF/WAO guideline recommendations have been implemented across Europe.

Methods

The EAACI Taskforce on CU in children, led by a group of expert clinicians and researchers in the field of pediatric CU, formulated a 35-question survey (Supplementary Table 1). A Survey Monkey questionnaire was circulated to 2,773 members of the EAACI Pediatric Section in November and December 2019. Four weeks was allowed for responding. At the same timeframe, the survey was also disseminated via EAACI social media channels, reaching an additional audience of 8,000 followers. The survey covered the following areas. First, characterization of the participating clinicians, particularly geographical location, professional background, type of practice and experience. Second and third were assessments of differences in diagnosis management practices including drug usage. The study protocol was approved by the Ethics Committee and Deontology of the University Hospital of Ioannina, Greece (approved number 8/7-5-2020 item 26 decision).

Statistical analysis

Due to anticipated differences in management between different parts of Europe, Eastern and Southern European countries (South) were compared to Western and Northern European (North) countries, based on The United Nations' geoscheme.[8] Differences between Northern and Southern European countries were assessed using chi-square tests with values of $P < 0.05$ being considered statistically significant.

Results

Participant characteristics

The survey was answered in total by 358 participants from 69 countries. The participants were mainly based in Europe (74.6%) followed by Asia (11.1%) and South America (8.4%). Less represented were clinicians from Africa (1.7%), North America (1.4%) and Australia (0.8%) (Supplementary Table 2). European participants were further divided into Northern Europe (n = 79) and Southern Europe (n = 179).

Most participants had a professional background in pediatric allergy (80%) or pediatrics (50%). Less frequent were allergists (25%), pediatric immunologists (14%), immunologists (5.3%) and dermatologists (1.4%). (Supplementary Table 3). Most participants work in

224 a public (district) (41.9%) or university (teaching) hospital (27%), while others work in a
225 private practice/clinic (19%) or private hospital (11%).
226 Participants see on average per month 5.6 CU patients 0–4 years old, 6.2 patients 5–
227 11 years old and 6.2 patients 12-18 old. Most clinicians (65%) indicated that they follow
228 EAACI/WAO/GA2LEN/EDF guidelines when diagnosing urticaria, and only 7.3%
229 responded that they do not follow any specific guidelines while others (20%) follow other
230 national guidelines. When comparing Northern and Southern Europe, both regions have a
231 preference to follow EAACI/WAO/Ga2LEN/EDF guidelines (57% and 74%). Nevertheless,
232 there was a significant (P = 0.012) preference to use National guidelines in the Northern
233 compared with Southern European countries (Table 1).
234

235 ***Diagnosis***

236 In the second part of the survey, clinicians were asked about patient's symptoms and
237 diagnostic methods used in CSU and CIndU.

238 Reports of associated angioedema varied widely, as shown in Figure 1. In summary,
239 36% of clinicians reported <10%, 35% reported 10-30%, 14% reported 31-50% and only 4%
240 reported 51-70%.
241 Considering the diagnosis of CSU, a summary of the individual tests applied by the
242 358 responding clinicians is shown in Figure 2. The most frequent baseline investigations
243 included: full blood count (FBC) 83%, thyroid profile (free triiodothyronine- fT3, thyroxine-
244 fT4, Thyroid Stimulating Hormone-TSH) 62%, total IgE 59%, thyroid antibodies
245 (antithyroglobulin, antithyroid peroxidase) 55%, and anti-nuclear antibody (ANA) or other
246 antibodies 51%. Very rarely, clinicians use the Basophil Activation Test (BAT, 2.5%) and
247 Basophil Histamine Release Assay (BHRA, 2.2%).
248 When diagnosing CU, there is a significant trend for Southern European countries to
249 use more routine tests than Northern countries. As shown in Figure 3, highly significant (P <
250 0.001) differences include full blood count, total IgE, antithyroid antibodies, parasitic
251 investigations and hepatitis serology. Full details of the tests are shown in Supplementary
252 Table 4.

253 Considering the allergological work-up (i.e., skin prick test for aeroallergens, specific
254 IgE to aeroallergens, specific IgE to food allergens, and skin prick test for food allergens),

48% of the participants indicated that they use at least one of these tests when evaluating children with CU the first time.

When CIndU is suspected, 58% of clinicians use the ice cube test and 49% a dermographometer. Interestingly, 23% of clinicians do not use a formal test to assess for CIndU (Table 2). Again, there was a significant (P = 0.019) trend for Southern versus Northern European countries to use more tests in the work-up of pediatric CIndU (Supplementary Table 5).

Patient management

When managing CU, most clinicians (60%) use a 2nd generation antihistamine (sgAH) at a dose adjusted for age/weight and some (7.8%) clinicians updose sgAH right away. Montelukast or topical steroids were almost never used as a first-line treatment (Table 3), while some clinicians (5.3%) still use a 1st generation antihistamine (fgAH) as their preferred first- line treatment. Most clinicians (63%) are aware that the half-life of chlorpheniramine, a fgAH, is around 24 hours and may still cause morning drowsiness while only 11% were not sure and 7.5% were completely unaware. Treating children under the age of 6 years is controversial with 39% of clinicians using cetirizine, 25% desloratadine and 7% rupatadine.

Time to move second- line treatment is 1-2 weeks for 27%, and 2-4 weeks for 37% of clinicians. The remainder waits for 4-6 weeks or even longer. As second-line treatment, 65% of clinicians choose to up-dose sgAH.

Similarly, the preferential waiting period, before moving to a third treatment step, is 1-2 weeks (21%) or 2-4 weeks (38%). As a third-line treatment, 22% of clinicians updose sgAH, 21% use omalizumab and 11% use montelukast. Cyclosporin A is almost never used (0.8%) and no one uses methotrexate or azathioprine.

Oral steroids as a therapeutic option for children with CU was chosen by 1.1% and 5.9% of participants as second-line and third-line treatment, respectively.

When selecting the appropriate drug for patient treatment, two thirds (75%) of the clinicians do not use off-label treatment, 2.5% indicated they do not remember, and only 2% use dapsone or 0.6% danazol.

When comparing the preferential treatment lines between countries, the preference for a sgAH as 1st line treatment and updosing a sgAH as second- and third-line treatments is consistent across all countries. However, there are significant (P = 0.001) differences in

preference for third-line of treatment between Southern and Northern European countries, (Supplementary Table 6). Specifically, fgAH and oral corticosteroids were used by 10% and 12% respectively by Southern European clinicians compared with 3.5% and 2% by Northern European clinicians.

In this survey, most clinicians (36%) do not use fgAH to aid sleep, 23% use them rarely and 1.7% use them regularly. Almost the 10% of Southern European clinicians are more likely to sometimes use fgAH to aid sleep compared with 3.5% of Northern European clinicians (P = 0.005).

Omalizumab is not used by any clinician as first- line treatment in CU, while 1.7% use it as second- and 21% as third-line treatment. However, of these clinicians, 65% and 71% prescribed omalizumab to less than 10% of their CSU patients and CIndU patients, accordingly. Omalizumab is used by 68% of clinicians in children of 12-18 years old, by 30% in 5-11 years old and by 1.4% in 0-4 years old. After administration, 35% of clinicians wait for 30 minutes and 27% 1 hour, while only 6.4% let the patients leave the clinic immediately. Respondents assess the treatment outcome between 3 months (28%) and 6 months (31%) of treatment. During the omalizumab treatment, 51% of clinicians continue treatment with antihistamines until the symptoms subside while 9.5% only treat every time the symptoms appear. After administration of omalizumab, it is frequent to see local signs at the injection site (40.5%) while only a few cases report cold or flu-like symptoms (10.9%) or body ache (5.9%). No cases of omalizumab-related anaphylaxis have been reported.

Additional management approaches

Regarding specific dietary recommendations, 55% of clinicians do not recommend any dietary modifications, but 14% recommend a low histamine diet and 9.2% pseudo-allergen- free diet. While 47% of clinicians do not routinely recommend drug restrictions, 24% advise NSAID and 3.9% ACE (angiotensin-converting-enzyme) inhibitor avoidance.

Furthermore, some clinicians use patient reported outcome measures (PROM), such as Urticaria Activity Score[9] used for 7 consecutive days (UAS7, 33%) or Urticaria Control Test[10] (UCT, 23%) to record patient outcome. But 31% do not use any PROMs. Assessment of the patients' QoL is done at every follow-up visit by 39% of respondents, although 21% of clinicians never assess QoL of their patients.

Patient transition

In the last part of the survey, clinicians were asked about their approach to transition care practice. Despite the need to change from a pediatric clinic to an adult clinic, 21% of clinicians do not have a transition service in collaboration with adult physicians. Furthermore, 20% only provide this service occasionally while only 17% always. Approximately 19% continue treating the patients as adults.

Discussion

This international survey, reporting on the diagnostic approach and management of CU in children, included participants from specialized centres in Europe, Asia and South America. Most respondents were pediatric allergists and pediatricians, and fewer were allergists and pediatric immunologists. The participants are predominantly based in Europe, and the majority work in public (district) or university (teaching) hospitals. Most clinicians (65%) follow EAACI/WAO/GA2LEN/EDF guidelines[7] when diagnosing children with urticaria. However, national guidelines are followed by some clinicians (18%), most of whom are from Northern Europe.

The majority (70%) of the clinicians reported that less than 30% of their patients suffered from angioedema. This is in line with other studies, that present a less frequent occurrence of angioedema in children with CU. [11-13],

While diagnosis is based primarily on clinical presentation, there is often a need for investigations to exclude a possible underlying cause. Regarding the work-up of CU patients, most clinicians use baseline investigations (FBC, thyroid profile and thyroid antibodies, IgE, ANA) and only 1/3 of the clinicians examined their CU patients for parasitic infections and celiac disease. This diagnostic work-up is in line with EAACI guidelines [7], as well as the British,[14] Italian [15] and Portuguese guidelines. [16] All these guidelines mention pediatric CU and the differences from adult CU. The list of the main guidelines in the field of chronic urticaria and the recommended diagnostic tests are summarized in Table 4. Furthermore, we noticed a significant trend of Southern European countries to use more routine diagnostic tests for CU. The BAT and BHRA were rarely used. The reasons for this are probably poor access, high cost and lack of awareness. Nevertheless, BAT has been suggested as an *in vitro* alternative for ASST, to diagnose, examine and predict patients with suspected CU. [17-19]

Sixty percent of clinicians, almost the same percentage who follow EAACI/WAO/GA2LEN/EDF guidelines, use a sgAH (age/weight-adjusted) which is a basic recommendation of the guidelines.[7] Five percent of participants still use a fgAH as their

353 preferred first-line treatment even though their 24 hours half-life and their causality of
354 drowsiness in the morning has been documented in the literature.[20, 21] In this study, 18% of
355 the physicians were little or not even aware of the sedative properties of fgAH.
356 A questionnaire study on the prevalence and treatment of pediatric urticaria in five
357 European countries revealed that there was significant use of oral steroids (10–28%)[13]. In a
358 US study involving adults and children, oral corticosteroids were the most commonly
359 prescribed medication, with 55% of patients requiring at least one course.[22] Interestingly, in
360 our survey, oral steroids are chosen only by 1% as the second-line and 6% as the third-line
361 treatment.
362 When comparing the preferential first-, second- and third-line of treatment between
363 countries, we see that the preference for a sgAH as first-line of treatment is consistent across
364 all countries. Furthermore, up-dosing sgAH as a second-and third-line of treatment is also
365 consistent across all countries.
366 According to this survey, three-quarters of clinicians prefer omalizumab as a 3rd line
367 treatment for CSU compared to less than 10% for CIndU. These discrepancies are attributed
368 to the current licensing indication and age cut-offs in many European countries according to
369 national regulations and that omalizumab is not licensed for CIndU in many European
370 countries. Omalizumab is the only approved add-on therapy for H_1-antihistamine-refractory
371 CSU[23] for children between 12-18 years, but this perspective again depends on the national
372 regulations.[24] The drug is well tolerated, apart from frequent but mild local reactions. No
373 omalizumab-related anaphylactic episode was reported.
374 To record patient outcome, tools, such as UCT and UAS7 are used to measure disease
375 control, guide treatment decisions and help to understand the burden and impact of CU on the
376 lives of children and their families.[9, 10] However, most PROMs have been validated and can
377 be used only by older children and adolescents [25], which may explain that many clinicians do
378 not use them.
379 A different, yet important, part of pediatric patient treatment is transition into adult
380 services. For most European countries the transition age is 16 years of age. Only one third of
381 clinicians provide transition services to their patients. This needs to be improved in line with
382 guidelines.[26, 27]
383 A limitation in this study is that data only indicates the location of the clinicians who
384 chose to respond and disproportionately were more from Southern Europe, compared to
385 Northern Europe. In addition, the questionnaire was only sent to pediatric section members
386 while in some countries, dermatologists treat children with CU. Dermatologists have

experience with tests for CIndU in adults as well as using PROMS and systemic treatments in adults. Also, not all allergists who follow both adults and pediatric patients are members of the pediatric section. The results may, therefore, have been different if the survey had been applied more broadly, including members from the EAACI's Dermatology Section. Furthermore, the study is biased by the retrospective nature of the survey, which hampers the reliability of some estimations. However, the lack of previous real-life data at European level and the international multicentre nature of the information are relevant strengths.

Conclusion

This study investigated the diagnostic approach and management of CU in children, mainly by European pediatricians and pediatric allergists working in public hospitals or universities. Clinicians frequently use baseline investigations for diagnosis and largely implement current guidelines. Even though a sgAH is preferred as first line treatment and its updosing is also consistent across all countries as a second- and third-line treatments, a few clinicians still use a fgAH as their preferred first line treatment, despite their side effects. The results of this survey strengthen the need to re-evaluate, update and standardize protocols on the diagnosis and management of CU in children.

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Table1. Place of practise and guidelines for diagnostics

	AAAAI practice parameter	EAACI/WAO/GA2LEN/EDF guidelines	National guidelines	No guidelines followed
Northern Europe	1%	57%	35%	7%

Southern Europe	2%	74%	15%	8%

Each value is the percentage of clinicians responding. AAAAI; American Academy of Allergy, Asthma & Immunology, EAACI: European Academy of Allergy and Clinical Immunology, EDF; European Dermatology Forum, GA^{2}LEN; Global Allergy and Asthma European Network, WAO; World Allergy Organization.

Table 2. Routinely used tests for chronic inducible urticaria (CIndU) when suspected. Participants were allowed to select more than one test type

Test	Number of participants	Percentage
Ice cube test (cold urticaria)	206	58%
Dermographometer (dermographism)	176	49%
No test	83	23%
Temp Test (cold and heat urticaria)	58	16%
Wet compress (acquagenic urticaria)	54	15%
Treadmill/hot bath (cholinergic)	46	12%
Delayed pressure testing	26	7.3%
Vortex (vibratory reactions)	18	5.0%
Other †	12	3.4%

†Other results include: “Dermographism without dermographometer”, “depending on symptoms and suspicion”, “exercise”, “Fric test”, “I refer them to dermatologists”, “Using hand or tongue depressor to induce dermographism”, “only if indicated”, “stroke by sharp object”

Table 3. Preferred first line treatment for chronic urticaria in children (N=358). Results are ordered by frequency of the preferred treatment

First line treatment	Frequency	Percentage
2nd generation antihistamines (age/weight-adjusted)	216	60.3%
Up dosed 2nd generation antihistamines right away	28	7.8%
1st generation antihistamines (age/weight-adjusted)	19	5.3%
Combination of these two generations	5	1.4%
Montelukast	3	0.8%
Topical Steroids	1	0.3%
No answer	86	24.0%

593 Table 4. Main guidelines in the field of chronic urticaria

List of the main guidelines in the field of chronic urticaria					
Guidelines	**Country**	**First Author**	**Year**	**Recommended tests and procedures for chronic urticaria**	
				Routine diagnostic tests	**Extended diagnostic tests**
German Guidelines[28]	Germany	Baurer A	2021	FBC, ESR and/or CRP	Laboratory test should be performed when history and clinical data suggest an eliciting factor or a systemic disease such as autoinflammatory diseases, IgE-mediated food allergy, throid gland pathologies
French Guidelines[29]	France	Hacard F	2021	No recommendation for diagnostic tests	
Korean Guideline[30]	Korea	Song WJ	2020	No recommendation for diagnostic tests	
ASCIA Guidelines[31]	Australia	Katelaris C	2020	Not recommended	Laboratory test should be performed when history and clinical data suggest a systemic disease such as urticarial vasculitis, urticaria pigmentosa, or autoinflammatory disorders/CAPS
Italian Guidelines[15]	Italy	Caffarelli C	2019	Not recommended	Laboratory test should be performed when history and clinical data suggest an eliciting factor or a systemic disease such as coeliac disease, vasculitis or auto-inflammatory conditions such as CAPS
EAACI/ GA²LEN/EDF/WAO guideline[7]	Europe	Zuberbier T	2018	FBC. ESR and/or CRP	• Test for infectious diseases (eg, *H. pylori*) • Functional auto-antibodies (eg, ASST) • Thyroid hormones and auto-antibodies • Allergy skin tests and/or allergen avoidance test/avoidance diet • Tests for severe systemic diseases (eg,tryptase) • Other (eg, skin lesion biopsy)
International Guidelines[32]	America Europe	Beck LA	2017	Not given any specific recommendation, the authors summarise and compare EAACI/GA²LEN/EDF/WAO guidelines and American guidelines	
Asian Guidelines[33]	Thailand	Kulthanan K	2016	FBC, ESR	•ASST • Test for *H. Pylori* • ANA, D-dimer • Stool examination for parasites • Specific IgE •Thyroid hormones and autoantibodies
Turkish Guidelines[34]	Turkey	Kocaturk Goncu E	2016	FBC, ESR, CRP	Based on history; • Infectious diseases (H. pylori etc.) • Thyroid hormones and auto-antibodies • Pseudo-allergen free diet for 3 weeks • Autologous serum skin test • Skin lesion biopsy
BSACI Guideline[14]	UK	Powell RJ	2015	Not recommended	Additional investigations if clinically indicated • Urinalysis • FBC • ESR • Liver function tests (add viral hepatitis screen if transaminases are abnormal) • Coeliac screen: Tissue transglutaminase IgA antibodies and/or endomysial IgA antibodies • Thyroid function and antithyroid antibodies

					• Cold, dermographism and pressure provocation tests • Elimination rechallenge diets • Antinuclear antibodies • Skin biopsy • C4 and C1 inhibitor quantitation (indicated for children, presenting with angioedema without urticaria) • Tests for current or post viral, bacterial or parasitic infections
American Guideline[35]	America	Bernstein JA	2014	FBC, ESR and/or CRP, liver enzymes, TSH	Based on patient circumstances, history, and physical exam: • Skin biopsy • Physical challenge tests • Complement activity tests • Stool analysis (ova and parasites) • Cryoglobulin levels • Serologic and/or skin testing for immediate hypersensitivity • Thyroid autoantibodies to: TSH receptor, thyroglobulin, thyroid peroxidase, and sodium/iodine symporter • Serum protein electrophoresis
Japanese Guidelines[36]	Japan	Hide M	2012	Not recommended if no apparent symptom except for urticaria was identified. ASST may prove the involvement of autoimmune mechanisms in a population of chronic urticaria.	Specific tests are recommended based on subtypes such as allergic urticaria, FDEIA, aspirin urticaria, physical urticarias, angioedema, urticaria vasculitis, urticaria pigmentosa, Schnitzler's syndrome, and CAPS

ANA; antinuclear antibody, ASST; autologous serum skin test, CAPS; Cryopirin-associated periodic fever, CCP;citrullinated protein, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate, FBC; full blood count, FDEIA; food-dependent exercise induced anaphylaxis, RF; rheumatoid factor, H. Pylori; Helicobacter pylori, IgA; immunoglobulin A, IgE;immunoglobulin E, TSH; thyroid-stimulating hormone

Figure Legends:

Figure 1. Percentage of chronic urticaria patients complain of angioedema as indicated by the respondents

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604 Figure 2. Routinely used tests in the work-up of pediatric chronic urticaria

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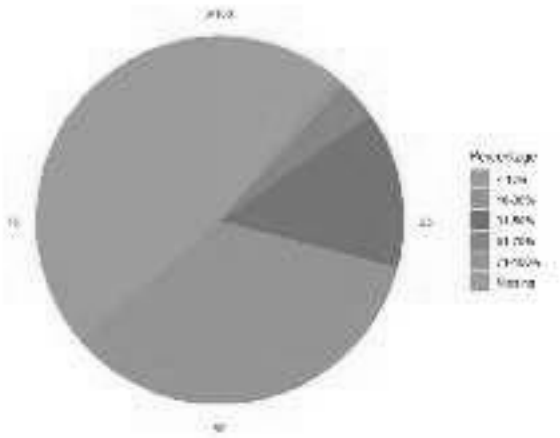
606 Figure 3. Routinely used tests in the work-up of pediatric chronic urticaria comparing
607 Northern European Countries (Blue, n=79) and Southern European Countries (Red, n=179).

Figure 1. Percentage of chronic urticaria patients complain of angioedema as indicated by the respondents



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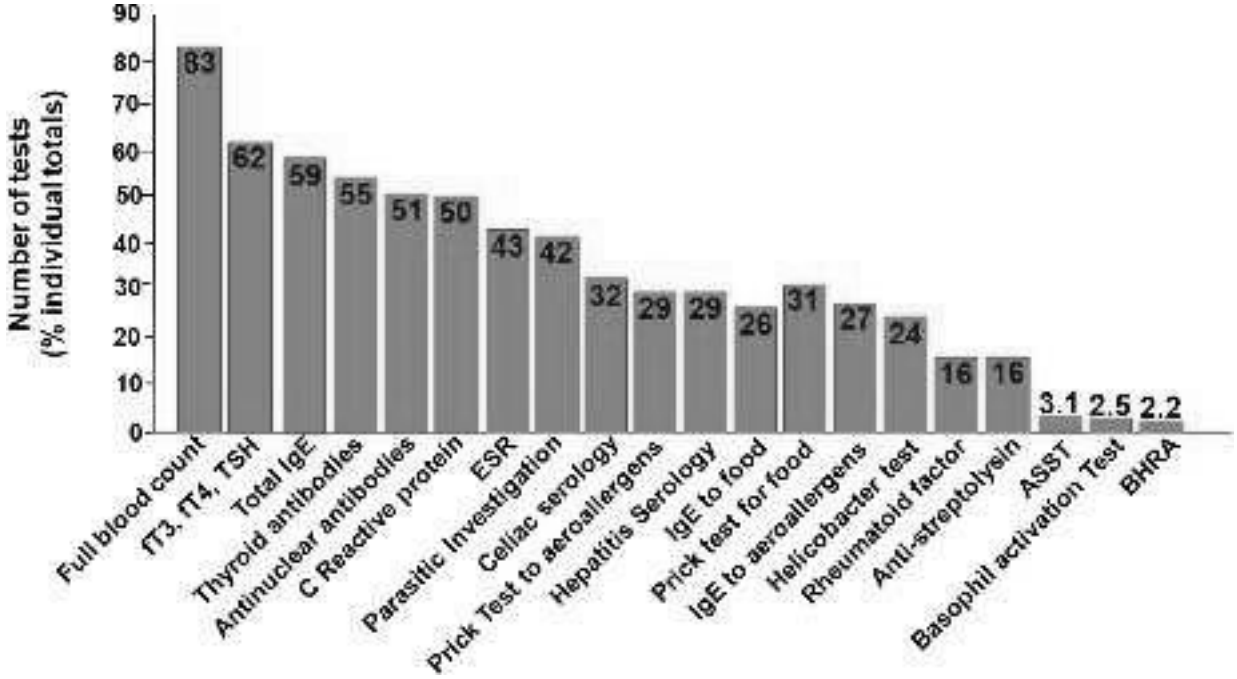

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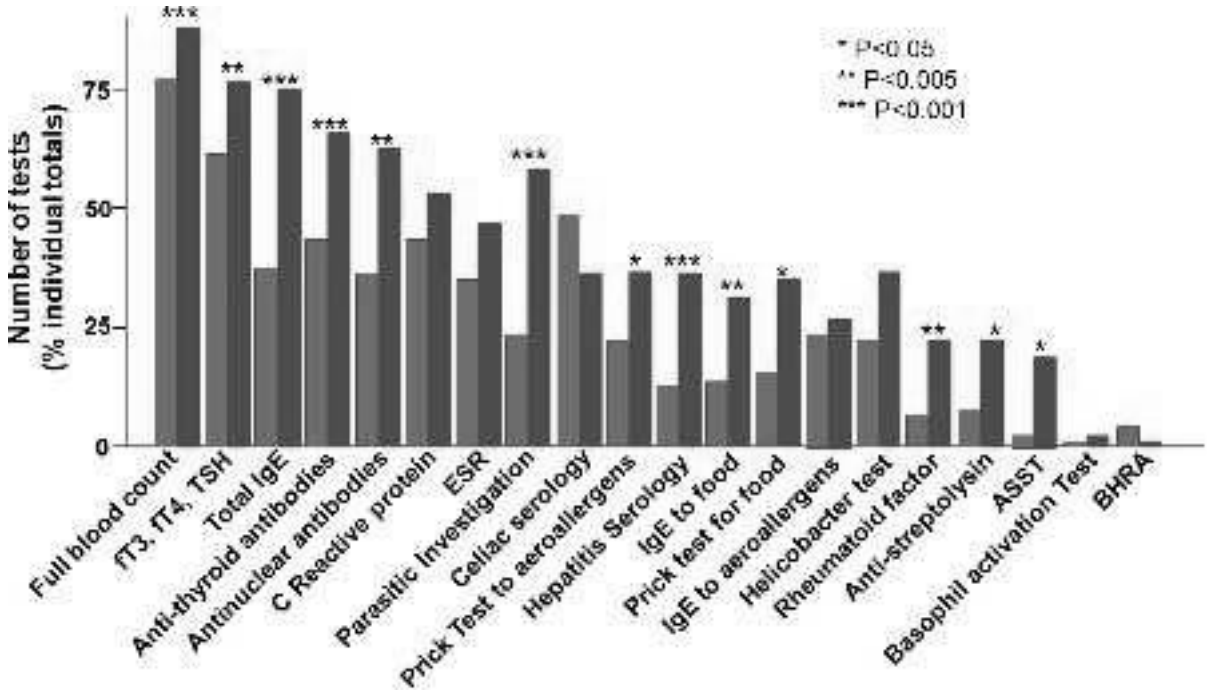

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