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

This is the peer reviewed version of the following article:

Original

A European survey of management approaches in chronic urticaria in children: EAACI pediatric urticaria taskforce / Tsabouri, S.; Arasi, S.; Beken, B.; Church, M. K.; Alvaro-Lozano, M.; Caffarelli, C.; Flohr, C.; Janmohamed, S. R.; Konstantinou, G. N.; Lau, S.; Lefevre, S.; Mortz, C. G.; Pajno, G.; Pite, H.; Rutkowski, K.; Staubach, P.; Van der Poel, L. -A.; Zuberbier, T.; Leslie, T. A.. - In: PEDIATRIC ALLERGY AND IMMUNOLOGY. - ISSN 0905-6157. - 33:(2022). [10.1111/pai.13674]

Availability:

This version is available at: 11381/2904263 since: 2022-01-12T18:16:23Z

Publisher:

John Wiley and Sons Inc

Published

DOI:10.1111/pai.13674

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note finali coverpage

(Article begins on next page)

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11 Article type : Original Article

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14 **A European survey of management approaches in chronic urticaria in children: EAACI**15 **Pediatric Urticaria Taskforce**

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/PAL.13674](https://doi.org/10.1111/PAL.13674)

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92 **Word count:** 2479

93 **Abstract : 248**

94 **Number of tables: 4**

95 **Number of supplementary tables: 6**

96 **Number of figures: 3**

97

98

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100

101

102

103

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110 **Conflict of Interests:**

111 MAL reports honoraria from advisory boards for Novartis and talks for Novartis, Uriach and
112 FAES Pharma (relevant to urticaria).

113 GNK and SRJ reports honoraria from advisory boards for Novartis (relevant to urticarial).

114 Non relevant honoraria from Pierre Fabre Benelux.

115 MKC has been a speaker or consultant for Almirall, FAES Pharma, Menarini, Moxie, MSD,
116 Novartis, UCB Pharma, Sanofi-Aventis and Uriach.

117 TL reports honoraria from advisory boards for Menlo and Novartis.

118 GNK and KR are giving lectures for Novartis

119 ST,SA, BB, CC, CF, CGM, GP, HP, LVDP, PS, SL, TZ have nothing to disclose.

120

121 **Funding:**

122 None of the authors perceived any fee for the present work. The online platform was
123 supported by an EAACI grant.

124

125 **Authors' contributions:**

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

132

133 **Abstract**

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

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

142 **Results:** The survey was sent to 2,773 physicians of whom 358 (13.8%) responded, mainly
143 pediatric allergists (80%) and pediatricians (49.7%), working in 69 countries. For diagnosis,
144 Southern European countries used significantly more routine tests (e.g., autoimmune testing,
145 allergological tests, and parasitic investigation) than Northern European countries. Most
146 respondents (60.3%) used a 2nd generation antihistamine as first- line treatment of whom
147 64.8% up dosed as a second- line. Omalizumab, was used as a second line treatment by 1.7%
148 and third-line by 20.7% of respondents. Most clinicians (65%) follow
149 EAACI/WAO/GA²LEN/EDF guidelines when diagnosing CU, and only 7.3% follow no
150 specific guidelines. Some clinicians prefer to follow national guidelines (18.4%, mainly
151 Northern European) or the AAAAI practice parameter (1.7%).

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

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

157

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

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

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

177

178

179 **Introduction**

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

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

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

194

195 **Methods**

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

207 **Statistical analysis**

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

213

214 **Results**

215 *Participant characteristics*

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

221 Most participants had a professional background in pediatric allergy (80%) or
222 pediatrics (50%). Less frequent were allergists (25%), pediatric immunologists (14%),
223 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),

255 48% of the participants indicated that they use at least one of these tests when evaluating
256 children with CU the first time.

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

262

263 *Patient management*

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

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

275 Similarly, the preferential waiting period, before moving to a third treatment step, is
276 1-2 weeks (21%) or 2-4 weeks (38%). As a third-line treatment, 22% of clinicians updose
277 sgAH, 21% use omalizumab and 11% use montelukast. Cyclosporin A is almost never used
278 (0.8%) and no one uses methotrexate or azathioprine.

279 Oral steroids as a therapeutic option for children with CU was chosen by 1.1% and
280 5.9% of participants as second-line and third-line treatment, respectively.

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

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

287 preference for third-line of treatment between Southern and Northern European countries,
288 (Supplementary Table 6). Specifically, fgAH and oral corticosteroids were used by 10% and
289 12% respectively by Southern European clinicians compared with 3.5% and 2% by Northern
290 European clinicians.

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

295 Omalizumab is not used by any clinician as first- line treatment in CU, while 1.7%
296 use it as second- and 21% as third-line treatment. However, of these clinicians, 65% and 71%
297 prescribed omalizumab to less than 10% of their CSU patients and CIndU patients,
298 accordingly. Omalizumab is used by 68% of clinicians in children of 12-18 years old, by 30%
299 in 5-11 years old and by 1.4% in 0-4 years old. After administration, 35% of clinicians wait
300 for 30 minutes and 27% 1 hour, while only 6.4% let the patients leave the clinic immediately.
301 Respondents assess the treatment outcome between 3 months (28%) and 6 months (31%) of
302 treatment. During the omalizumab treatment, 51% of clinicians continue treatment with
303 antihistamines until the symptoms subside while 9.5% only treat every time the symptoms
304 appear. After administration of omalizumab, it is frequent to see local signs at the injection
305 site (40.5%) while only a few cases report cold or flu-like symptoms (10.9%) or body ache
306 (5.9%). No cases of omalizumab-related anaphylaxis have been reported.

307

308 *Additional management approaches*

309 Regarding specific dietary recommendations, 55% of clinicians do not recommend
310 any dietary modifications, but 14% recommend a low histamine diet and 9.2% pseudo-
311 allergen- free diet. While 47% of clinicians do not routinely recommend drug restrictions,
312 24% advise NSAID and 3.9% ACE (angiotensin-converting-enzyme) inhibitor avoidance.

313 Furthermore, some clinicians use patient reported outcome measures (PROM), such
314 as Urticaria Activity Score⁹ used for 7 consecutive days (UAS7, 33%) or Urticaria Control
315 Test¹⁰ (UCT, 23%) to record patient outcome. But 31% do not use any PROMs. Assessment
316 of the patients' QoL is done at every follow-up visit by 39% of respondents, although 21% of
317 clinicians never assess QoL of their patients.

318

319 **Patient transition**

320 In the last part of the survey, clinicians were asked about their approach to transition
321 care practice. Despite the need to change from a pediatric clinic to an adult clinic, 21% of
322 clinicians do not have a transition service in collaboration with adult physicians. Furthermore,
323 20% only provide this service occasionally while only 17% always. Approximately 19%
324 continue treating the patients as adults.

325

326 **Discussion**

327 This international survey, reporting on the diagnostic approach and management of
328 CU in children, included participants from specialized centres in Europe, Asia and South
329 America. Most respondents were pediatric allergists and pediatricians, and fewer were
330 allergists and pediatric immunologists. The participants are predominantly based in Europe,
331 and the majority work in public (district) or university (teaching) hospitals. Most clinicians
332 (65%) follow EAACI/WAO/GA2LEN/EDF guidelines⁷ when diagnosing children with
333 urticaria. However, national guidelines are followed by some clinicians (18%), most of whom
334 are from Northern Europe.

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

338 While diagnosis is based primarily on clinical presentation, there is often a need for
339 investigations to exclude a possible underlying cause. Regarding the work-up of CU patients,
340 most clinicians use baseline investigations (FBC, thyroid profile and thyroid antibodies, IgE,
341 ANA) and only 1/3 of the clinicians examined their CU patients for parasitic infections and
342 celiac disease. This diagnostic work-up is in line with EAACI guidelines⁷, as well as the
343 British,¹⁴ Italian¹⁵ and Portuguese guidelines.¹⁶ All these guidelines mention pediatric CU
344 and the differences from adult CU. The list of the main guidelines in the field of chronic
345 urticaria and the recommended diagnostic tests are summarized in Table 4. Furthermore, we
346 noticed a significant trend of Southern European countries to use more routine diagnostic
347 tests for CU. The BAT and BHRA were rarely used. The reasons for this are probably poor
348 access, high cost and lack of awareness. Nevertheless, BAT has been suggested as an *in vitro*
349 alternative for ASST, to diagnose, examine and predict patients with suspected CU.¹⁷⁻¹⁹

350 Sixty percent of clinicians, almost the same percentage who follow
351 EAACI/WAO/GA2LEN/EDF guidelines, use a sgAH (age/weight-adjusted) which is a basic
352 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 H₁-antihistamine-refractory
371 CSU²³ 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 adolescents²⁵, 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

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

394

395 **Conclusion**

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

404

405 **Acknowledgements**

406 The authors acknowledge the financial support of EAACI. The EAACI Task Force on
407 Chronic Urticaria in children would like to thank the Executive Committee of the EAACI for
408 their constructive, expert review and Ana Antunes for her help with proofreading this paper .

409

410 **References**

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Table1. Place of practise and guidelines for diagnostics

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	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%

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547 Each value is the percentage of clinicians responding. AAAAI; American Academy of
548 Allergy, Asthma & Immunology, EAACI: European Academy of Allergy and Clinical
549 Immunology, EDF; European Dermatology Forum, GA²LEN; Global Allergy and Asthma
550 European Network, WAO; World Allergy Organization.

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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

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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, thyroid 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	Katellaris 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/GA ² LEN/EDF/WAO guideline ⁷	Europe	Zuberbier T	2018	FBC, ESR and/or CRP	<ul style="list-style-type: none"> • Test for infectious diseases (eg, <i>H. pylori</i>) • 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/GA ² LEN/EDF/WAO guidelines and American guidelines	
Asian Guidelines ³³	Thailand	Kulthanan K	2016	FBC, ESR	<ul style="list-style-type: none"> • ASST • Test for <i>H. Pylori</i> • 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; <ul style="list-style-type: none"> • Infectious diseases (<i>H. pylori</i> 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 <ul style="list-style-type: none"> • 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

					<ul style="list-style-type: none"> • 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	<p>Based on patient circumstances, history, and physical exam:</p> <ul style="list-style-type: none"> • Skin biopsy • Physical challenge tests • Complement activity tests • Stool analysis (ova and parasites)
<p><i>ANA; antinuclear antibody, ASST; autologous serum skin test, CAPS; Cryopyrin-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</i></p>					
					<ul style="list-style-type: none"> • 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

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599 **Figure Legends:**

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

602 respondents

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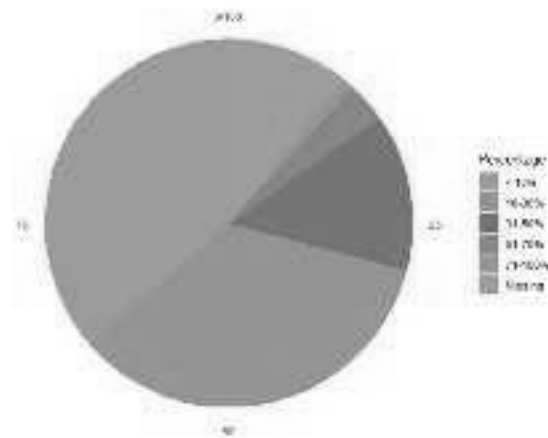
604 Figure 2. Routinely used tests in the work-up of pediatric chronic urticaria

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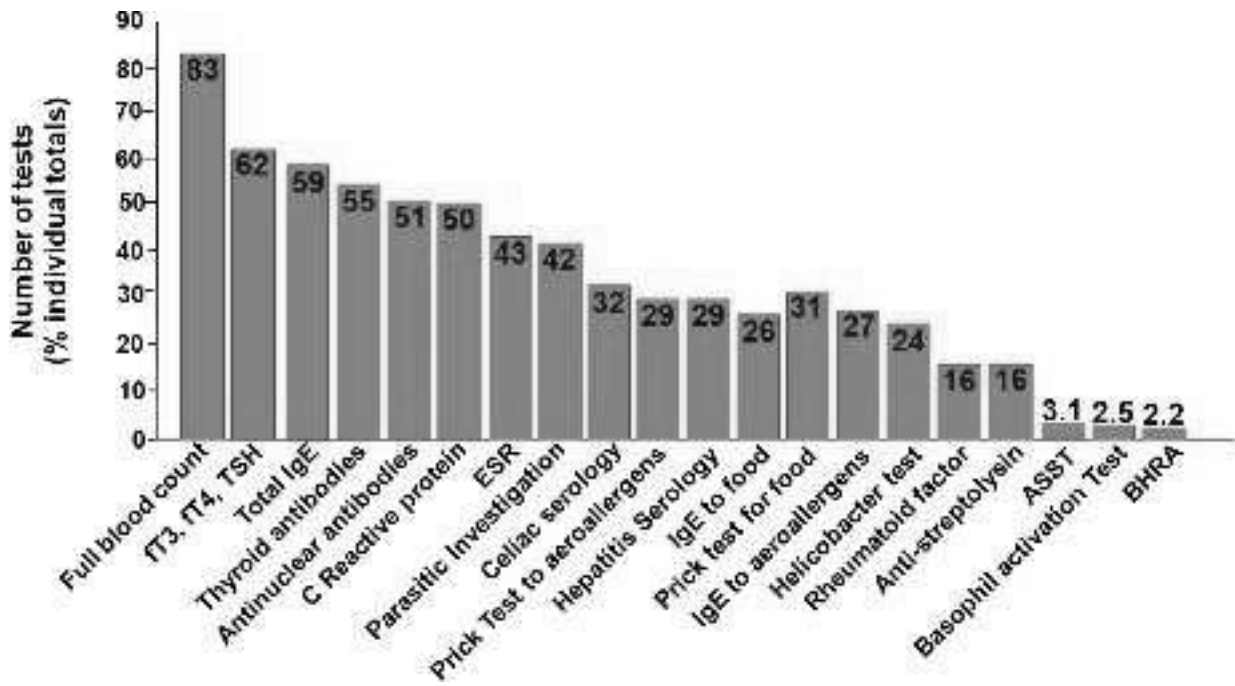
606 Figure 3. Routinely used tests in the work-up of pediatric chronic urticaria comparing

607 Northern European Countries (Blue, n=79) and Southern European Countries (Red, n=179).

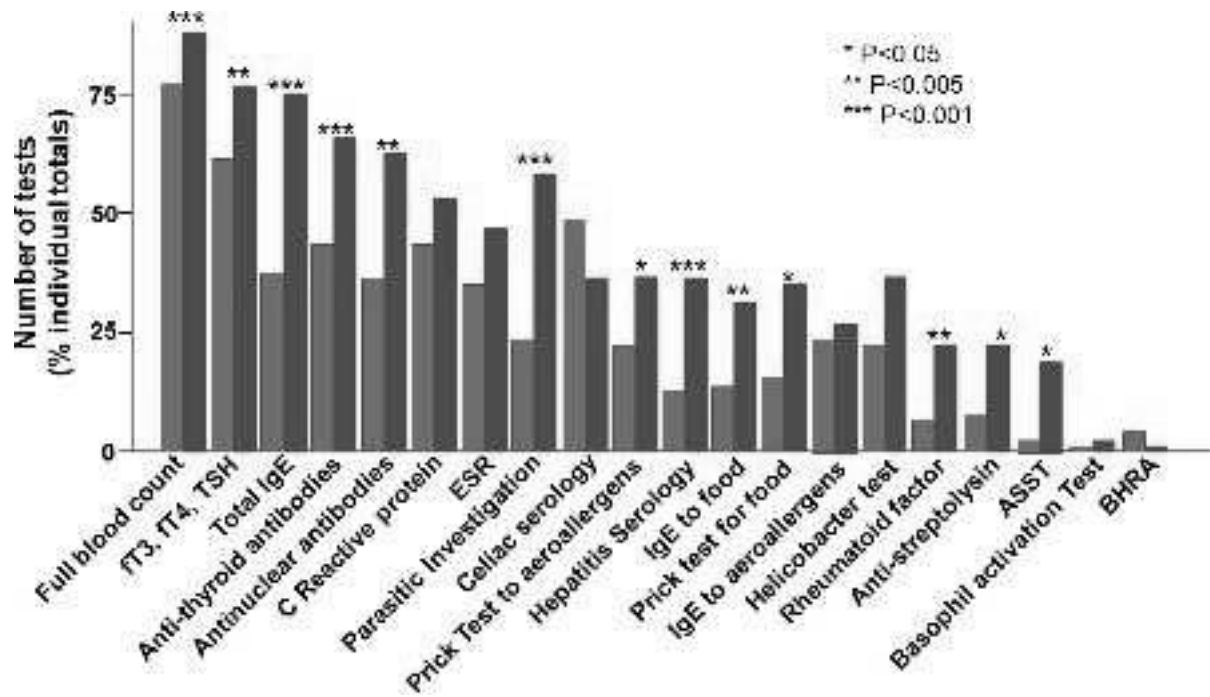
Figure 1. Percentage of chronic urticaria patients complain of angioedema as indicated by the respondents



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