

Correspondence: Luis Felipe Ensina, Department of Pediatrics, Division of Allergy, Clinical Immunology and Rheumatology, Federal University of São Paulo, Rua Barata Ribeiro, 490 - CJ. 67, São Paulo - SP 01308-000, Brazil (100alergia@gmail.com).

REFERENCES

1. Balp MM, Weller K, Carboni V, et al. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. *Pediatr Allergy Immunol*. 2018; <https://doi.org/10.1111/pai.12910>
2. Jares EJ, Sanchez-Borges M, Cardona-Villa R, et al. Multinational experience with hypersensitivity drug reactions in Latin America. *Ann Allergy Asthma Immunol*. 2014;113:282-289.
3. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update. *Allergy*. 2018;73:1393-1414.
4. Maurer M, Church MK, Gonçalo M, Sussman G, Sánchez-Borges M. Management and treatment of chronic urticaria (CU). *J Eur Acad Dermatol Venereol*. 2015;29(Suppl 3):16-32.
5. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868-887.

DOI: 10.1111/pai.12963

Reply to Ensina et al

To the Editor,

Thank you for the opportunity to respond to the interesting letter of Ensina et al¹ sent in reference to our recent manuscript (Balp et al²). The two studies by Balp et al and Ensina et al had different objectives and were conducted in different geographical areas using different methodologies. Our study (Balp et al) reported diagnosed prevalence, clinical characteristics, and treatment patterns in pediatric patients (aged 0-17 years) with chronic spontaneous urticaria (CSU) in five European countries (United Kingdom, Germany, Italy, France, and Spain). It was a physician-based online survey with physicians recruited from a large and representative panel among these five European countries (conducted during September-October 2015). A total of 2074 physicians completed the screener questionnaire designed to estimate national prevalence of diagnosed CSU, and 1127 physicians completed the main questionnaire designed to collect data on CSU disease characteristics and treatments. The study included all relevant medical specialties that are likely to see, manage, and treat pediatric patients with CSU. The results reflect the real-world evidence and clinical practice across different specialties (GPs, pediatricians, dermatologists, and allergists) and not only specialized centers.

The study by Ensina et al aimed to describe and compare disease characteristics and treatment patterns in adults and children with CSU. The data were obtained from a retrospective analysis of medical records of patients treated at a GA²LEN Urticaria Center of Reference and Excellence (UCARE),³ Federal University of São Paulo, São Paulo, Brazil, from April 2016 to June 2017, and included a total of 113 CSU patients and among them 31 pediatric patients aged 0-17 years.

Both studies are valuable and contribute to the overall knowledge about CSU in the pediatric population, but are not directly comparable as outlined above. The small sample size of pediatric

CSU patients (N = 31) in the study by Ensina et al might limit the external validity. Nevertheless, Ensina et al provided important insights regarding gender-specific differences in disease prevalence, presence of comorbidities (atopy and autoimmunity), presence of angioedema, hypersensitivity associated with nonsteroidal anti-inflammatory drugs (NSAIDs), treatment patterns, and response to treatments in pediatric CSU patients in their UCARE center in Brazil. Particularly, differences between pediatric and adult patients were reported. There is limited comparative information available in the literature regarding clinical characteristics and disease management of CSU in pediatric patients.^{4,5} Therefore, the findings provided by Ensina et al are very relevant.

In our study, 5%-14% of pediatric CSU patients of the representative cohort had angioedema according to physician recall and report, whereas Ensina et al reported that 58% of patients seen in their center had angioedema. Another study by Volonakis et al, which investigated 226 pediatric urticaria patients aged 1-14 years, reported that wheals along with angioedema were present in 15% of patients.⁶ One major reason for these differences in angioedema prevalence could be that patients seen in a center of reference tend to have more severe disease compared to those seen in general practices by GPs, private clinics, and general hospitals. Ensina et al also highlighted this point. Moreover, the data reported by patients and physicians tend to be discrepant.⁷ Regarding angioedema, another study in CSU emphasized this difference in reporting between physicians and patients.⁸ In terms of prevalence of CSU, our study calculated diagnosed prevalence via extrapolating to the general pediatric population from a representative panel in five countries, whereas the study by Ensina et al presented the data relevant to the UCARE center.

The use of H1-antihistamines and response to treatment were reported in both studies. Ensina et al reported that the majority of pediatric patients received H1-antihistamine treatment, with 35% of

patients receiving H1-antihistamines at approved doses and 52% patients at higher than approved doses. In our study, 42%-65% of pediatric CSU patients received H1-antihistamines at approved doses, whereas 16%-51% at higher than approved doses. The reported range is based on different age-groups (0-6, 7-11, and 12-17 years) and five countries. We see differences in usage patterns of H1-antihistamines even between five European countries, so differences in usage of H1-antihistamines are expected when comparing Europe and Brazil. Nevertheless, both studies report that the majority of patients are treated with H1-antihistamines (at approved or higher doses). Ensina et al reported that 23% of pediatric CSU patients did not respond to H1-antihistamine treatment at approved or higher doses. In our study, 21%-43% of pediatric patients (based on country and three different age-groups) remained uncontrolled with H1-antihistamines treatment at approved or higher doses, which is similar to the findings reported by Ensina et al.

There are several unanswered questions regarding CSU in children, which include disease prevalence across the world, clinical patterns, underlying causes, impact on everyday life of the disease in children, and the natural course of disease in pediatric patients.^{4,5} It is necessary that further studies are conducted at multiple centers and at national/international level to better understand the disease, obtain accurate prevalence and incidence estimates, explore, and understand differences between different geographies. Several ongoing initiatives may be helpful for addressing these aspects. The work of GA²LEN UCAREs and the UCARE network is important to improve the management and to increase the knowledge of urticaria by research and education.³ Registries such as CURE, the chronic urticaria registry (<http://www.urticaria-registry.com>), and international meetings on urticaria such as the Global Urticaria Forum (<https://www.globalurticariaforum.org/home/>) are important tools to jointly improve our knowledge and the awareness of urticaria, particularly in pediatric patients.

ORCID

Maria-Magdalena Balp  <http://orcid.org/0000-0002-8612-7680>

Maria-Magdalena Balp¹ 
Karsten Weller²

Veruska Carboni³
Alexandra Chirilov⁴
Charis Papavassilis¹
Thomas Severin¹
Haijun Tian⁵
Torsten Zuberbier²
Marcus Maurer²

¹Novartis Pharma AG, Basel, Switzerland

²Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Berlin, Germany

³GfK Switzerland AG, Risch-Rotkreuz, Switzerland

⁴GfK SE, Nuremberg, Germany

⁵Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

Correspondence: Maria-Magdalena Balp, Novartis Pharma AG, Basel, Basel-Stadt, Switzerland (maria-magdalena.balp@novartis.com).

REFERENCES

1. Ensina LF, Bastos PGA, de Lacerda AE, de Araujo CA, Camelo-Nunes I, Sole D. Chronic urticaria in children may be different from adults. *Pediatr Allergy Immunol*. 2018;29:669-670.
2. Balp MM, Weller K, Carboni V, et al. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. *Pediatr Allergy Immunol*. 2018;29:670-671.
3. Maurer M, Metz M, Bindslev-Jensen C, et al. Definition, aims, and implementation of GA(2) LEN urticaria centers of reference and excellence. *Allergy*. 2016;71:1210-1218.
4. Church MK, Weller K, Stock P, Maurer M. Chronic spontaneous urticaria in children: itching for insight. *Pediatr Allergy Immunol*. 2011;22:1-8.
5. Maurer M, Church MK, Weller K. Chronic urticaria in children – still itching for insight. *JAMA Dermatol*. 2017;153:1221-1222.
6. Volonakis M, Katsarou-Katsari A, Stratigos J. Etiologic factors in childhood chronic urticaria. *Ann Allergy*. 1992;69:61-65.
7. Weller K, Peveling-Oberhag A, Schoepke N, Zuberbier T, Staubach P, Maurer M. Instrumente zur Erfassung von Krankheitsaktivität, Krankheitskontrolle und Lebensqualitätsbeeinträchtigung bei Patienten mit chronischer Urtikaria und Angioödem. *Allergologie*. 2016;39:6-15.
8. Sussman G, Abuzakouk M, Berard F, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: analyses from ASSURE-CSU. *Allergy*. 2018;73:1724-1734.