Received: 24 June 2021 | Revised: 31 August 2021 | Accepted: 6 September 2021

DOI: 10.1111/all.15090

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

GUIDELINES

The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria

Torsten Zuberbier[1] | Amir Hamzah Abdul Latiff[2] | Mohamed Abuzakouk[3] | Susan Aquilina[4] | Riccardo Asero[5] | Diane Baker[6] | Barbara Ballmer-Weber[7,8] | Christine Bangert[9] | Moshe Ben-Shoshan[10] | Jonathan A. Bernstein[11] | Carsten Bindslev-Jensen[12] | Knut Brockow[13] | Zenon Brzoza[14] | Herberto Jose Chong Neto[15] | Martin K. Church[1,16] | Paulo R. Criado[17] | Inna V. Danilycheva[18] | Corinna Dressler[19] | Luis Felipe Ensina[20] | Luz Fonacier[21] | Matthew Gaskins[19] | Krisztian Gáspár[22] | Aslı Gelincik[23] | Ana Giménez-Arnau[24] | Kiran Godse[25] | Margarida Gonçalo[26] | Clive Grattan[27] | Martine Grosber[28] | Eckard Hamelmann[29] | Jacques Hébert[30] | Michihiro Hide[31,32] | Allen Kaplan[33] | Alexander Kapp[34] | Aharon Kessel[35] | Emek Kocatürk[36] | Kanokvalai Kulthanan[37] | Désirée Larenas-Linnemann[38] | Antti Lauerma[39] | Tabi A. Leslie[40] | Markus Magerl[1,41] | Michael Makris[42] | Raisa Y. Meshkova[43] | Martin Metz[1,41] | Daniel Micallef[4] | Charlotte G. Mortz[44] | Alexander Nast[19] | Hanneke Oude-Elberink[45] | Ruby Pawankar[46] | Paolo D. Pigatto[47] | Hector Ratti Sisa[48] | María Isabel Rojo Gutiérrez[49] | Sarbjit S. Saini[50] | Peter Schmid-Grendelmeier[51] | Bulent E. Sekerel[52] | Frank Siebenhaar[1,41] | Hanna Siiskonen[53] | Angele Soria[54] | Petra Staubach-Renz[55] | Luca Stingeni[56] | Gordon Sussman[57] | Andrea Szegedi[22] | Simon Francis Thomsen[58] | Zahava Vadasz[59] | Christian Vestergaard[60] | Bettina Wedi[61] | Zuotao Zhao[62] | Marcus Maurer[1,41]

Abbreviations: AAS, Angioedema activity score; ACARE, Angioedema Center of Reference and Excellence; ACE, Angiotensin-converting enzyme; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; AGREE, Appraisal of Guidelines Research and Evaluation; AH, Antihistamine; AOSD, Adult-onset Still's disease; APAAACI, Asia Pacific Association of Allergy, Asthma and Clinical Immunology; ARIA, Allergic Rhinitis and Its Impact on Asthma; ASST, Autologous Serum Skin Test; BAT, Basophil activation test; BHRA, Basophil histamine release assay; CAPS, Cryopyrin-associated periodic symptoms; CIndU, Chronic inducible urticaria; CNS, Central nervous system; CSU, Chronic spontaneous urticaria; CU, Chronic urticaria; CU-Q2oL, Chronic urticaria Quality of Life Questionnaire; CYP, Cytochrome P; EAACI, European Academy of Allergology and Clinical Immunology; EDF, European Dermatology Forum; EtD, Evidence-to-Decision; FCAS, Familial Cold Autoinflammatory Syndrome; GA²LEN, Global Asthma and Allergy European Network; GDT, Guideline Development Tool; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HAE, Hereditary angioedema; HIDS, Hyper-IgD syndrome; IVIG (also IGIV), Intravenous immunoglobulins; MWS, Muckle-Wells-Syndrome; NOMID, Neonatal Onset Multisystem Inflammatory Disease; NSAID, Non-steroidal anti-inflammatory drugs; PAF, Platelet-activating factor; PET, Positron Emission Tomography; PICO, Technique used in Evidence-based Medicine, acronym stands for Patient/Problem/Population, Intervention, Comparison/Control/Comparator, Outcome; PROM, Patient-reported outcome measure; REM, Rapid eye movement; sJIA, Systemic-onset juvenile idiopathic arthritis; TRAPS, Tumor necrosis factor receptor alpha-associated periodic syndrome; UAS, Urticaria activity score; UCARE, Urticaria Center of Reference and Excellence; UCT, Urticaria Control Test; UEMS, European Union of Medical Specialists; UV, Ultraviolet; WHO, World Health Organization.

[1]Comprehensive Allergy Centre Charité, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[2]Allergy & Immunology Centre, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

[3]Department of Allergy and Immunology, Respiratory Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

[4]Department of Dermatology, Mater Dei Hospital, Msida, Malta

[5]Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy

[6]Baker Allergy, Asthma and Dermatology, Portland, Oregon, USA

[7]Clinic for Dermatology and Allergology, Kantonsspital St. Gallen, St. Gallen, Switzerland

[8]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

[9]Department of Dermatology, Medical University of Vienna, Vienna, Austria

[10]Division of Allergy, Immunology and Dermatology, Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada

[11]University of Cincinnati Physicians Immunology Research Center, Cincinnati, OH, USA

[12]Department of Dermatology and Allergy Centre, Odense University Hospital and University of Southern Denmark, Odense, Denmark

[13]Department of Dermatology and Allergy Biederstein, Faculty of Medicine, Technical University Munich, Munich, Germany

[14]Department of Internal Diseases with Division of Allergology, University of Opole, Opole, Poland

[15]Division of Allergy and Immunology, Department of Pediatrics, Federal University of Paraná, Curitiba, Brazil

[16]University of Southampton, Southampton, UK

[17]Sociedade Brasileira de Dermatologia (SBD), Centro Universitário FMABC, Alergoskin (UCARE), Santo André, Brazil

[18]Department of Allergology and Immunotherapy, National Research Center-Institute of Immunology Federal Medical-Biological Agency of Russia, Moscow, Russia

[19]Division of Evidence-Based Medicine, Department of Dermatology, Venereology and Allergy, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[20]Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil

[21]New York University Long Island School of Medicine, New York, New York, USA

[22]Division of Dermatological Allergology, Department of Dermatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

[23]Division of Immunology and Allergic Diseases, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

[24]Department of Dermatology, Hospital del Mar, Institut Mar d'Investigacions Mèdiques, Universitat Autònoma y Universitat Pompeu Fabra, Barcelona, Spain

[25]Department of Dermatology, D Y Patil University School of Medicine, Navi Mumbai, India

[26]Department of Dermatology, Coimbra University Hospital and Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[27]Guy's Hospital, St John's Institute of Dermatology, London, UK

[28]Department of Dermatology, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium

[29]Department of Pediatrics, Children's Center Bethel, University Hospital OWL, University Bielefeld, Bielefeld, Germany

[30]Service d'allergie, Centre Hospitalier Université Laval/Centre Hospitalier Universitaire de Québec, Québec, Quebec, Canada

[31]Department of Dermatology, Hiroshima University, Hiroshima, Japan

[32]Department of Dermatology, Hiroshima Citizens Hospital, Hiroshima, Japan

[33]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Medical University of South Carolina, Charleston, South Carolina, USA

[34]Department of Dermatology & Allergy, Hannover Medical School (MHH), Hannover, Germany

[35]Division of Allergy and Clinical Immunology, Bnai Zion Medical Center and the Bruce and Ruth Rappaport Faculty of Medicine, Technion, Haifa, Israel

[36]Department of Dermatology, Koç University School of Medicine, Istanbul, Turkey

[37]Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[38]Hospital Médica Sur, Mexico City, Mexico

[39]Department of Dermatology, Allergology and Venereology, Inflammation Centre, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[40]Department of Dermatology, Royal Free Hospital, London, UK

[41]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany

[42]Allergy Unit, 2nd Department of Dermatology and Venereology, National and Kapodistrian University of Athens, University General Hospital "Attikon", Athens, Greece

[43]Department of Clinical Immunology and Allergology, Smolensk State Medical University, Smolensk, Russia

[44]Department of Dermatology and Allergy Centre, Odense Research Center for Anaphylaxis (ORCA), Odense University Hospital and University of Southern Denmark, Odense, Denmark

[45]University of Groningen, Groningen, The Netherlands

[46]Department of Pediatrics, Nippon Medical School, Tokyo, Japan

[47]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

[48]Primera Cátedra de Clínica Médica, Hospital de Clínicas de la Facultad de Ciencias Médicas-Universidad Nacional de Asunción, Asunción, Paraguay

[49]Hospital Juárez de México, Mexico City, Mexico
[50]Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland, USA
[51]Allergy Unit, Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland
[52]Division of Pediatric Allergy and Asthma, Hacettepe University Faculty of Medicine, Ankara, Turkey
[53]Department of Pathology, Diagnostic Imaging Centre, Kuopio University Hospital, Kuopio, Finland
[54]Department of Dermatology and Allergology, Tenon Hospital, APHP Sorbonne University and Cimi-Paris Inserm 1135, Paris, France
[55]Department of Dermatology, University Medical Center Mainz, Mainz, Germany
[56]Dermatology Section, Department of Medicine, University of Perugia, Perugia, Italy
[57]Division of Allergy and Clinical Immunology, St. Michael's Hospital and University of Toronto, Toronto, Canada
[58]Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark
[59]Proteomic and Clinical Flow Cytometry Unit, Bnai Zion Medical Center, Rappaport Faculty of Medicine, Technion, Haifa, Israel
[60]Department of Dermatology and Venereology, Aarhus University Hospital, Aarhus, Denmark
[61]Department of Dermatology and Allergy, Comprehensive Allergy Center, Hannover Medical School, Hannover, Germany
[62]Department of Dermatology and Venereology, Peking University First Hospital, Beijing, China

Correspondence
Torsten Zuberbier, Comprehensive Allergy Centre Charité, Charité – Universitätsmedizin Berlin, Hindenburgdamm 30, 12203 Berlin, Germany.
Email: torsten.zuberbier@charite.de

Funding information
Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs); Global Allergy and Asthma European Network (GA²LEN); European Academy of Allergology and Clinical Immunology (EAACI); Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI); European Dermatology Forum (EDF)

Abstract

This update and revision of the international guideline for urticaria was developed following the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. It is a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF; EuroGuiDerm), and the Asia Pacific Association of Allergy, Asthma and Clinical Immunology with the participation of 64 delegates of 50 national and international societies and from 31 countries. The consensus conference was held on 3 December 2020. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS). Urticaria is a frequent, mast cell–driven disease that presents with wheals, angioedema, or both. The lifetime prevalence for acute urticaria is approximately 20%. Chronic spontaneous or inducible urticaria is disabling, impairs quality of life, and affects performance at work and school. This updated version of the international guideline for urticaria covers the definition and classification of urticaria and outlines expert-guided and evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria.

KEYWORDS
angioedema, consensus, evidence-based, hives, itch, mast cell, urticaria, wheal

1 | INTRODUCTION

This update and revision of the international guideline for urticaria is based on evidence and expert consensus and was developed following the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. A structured consensus process was used to discuss and agree upon recommendations. The conference was held in a hybrid format on 3 December 2020, in Berlin, Germany and online.

The guideline is a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF), and the Asia Pacific Association of Allergy, Asthma, and Clinical Immunology (APAAACI). All of these organizations provided funding for the development of the guideline, which is an update and revision of the EAACI/GA²LEN/EDF/WAO guideline on urticaria published in 2018.[1–4] There was no funding from other sources.

TABLE 1 Members of the expert panel

Title	First name	Last name	Country	Nominating society	Affiliations	Role
Dr.	Amir Hamzah	Abdul Latiff	Malaysia	Malaysian Society of Allergy and Immunology (MSAI)	Allergy & Immunology Centre, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia	Co-author
Prof. Dr.	Mohamed	Abuzakouk	United Arab Emirates	Pan Arab Society of Allergy, Asthma and Immunology (PASAAI)	Department of Allergy and Immunology, Respiratory Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates	Co-author
Dr.	Susan	Aquilina	Malta	Maltese Association of Dermatology & Venereology (MADV)	Department of Dermatology, Mater Dei Hospital, Msida, Malta	Co-author
Prof. Dr.	Riccardo	Asero	Italy	Italian Association of Hospital and Territorial Allergists and Immunologists (AAIITO)	Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy	Co-author
Dr.	Diane R.	Baker	USA	American Academy of Dermatology (AAD)	Baker Allergy, Asthma and Dermatology, Portland, Oregon, USA	Co-author
Prof. Dr.	Barbara	Ballmer-Weber	Switzerland	Swiss Society for Allergology and Immunology (SGAI)	Clinic for Dermatology and Allergology, Kantonsspital St. Gallen, St.Gallen, Switzerland; Department of Dermatology, University Hospital Zurich, Zurich, Switzerland	Co-author
Dr.	Christine	Bangert	Austria	Austrian Society of Dermatology and Venereology (ÖGDV)	Department of Dermatology, Medical University of Vienna, Vienna, Austria	Co-author
Prof. Dr.	Moshe	Ben-Shoshan	Canada	Canadian Society of Allergy and Clinical Immunology (CSACI)	Division of Allergy, Immunology and Dermatology, Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada	Co-author
Prof. Dr.	Jonathan A.	Bernstein	USA	Global Allergy and Asthma European Network (GA²LEN)	University of Cincinnati Physicians Immunology Research Center, Cincinnati, OH, USA	Co-author
Prof. Dr.	Carsten	Bindslev-Jensen	Denmark	Danish Society for Allergology (DSA), European Academy of Allergy and Clinical Immunology (EAACI)	Department of Dermatology and Allergy Centre, Odense University Hospital and University of Southern Denmark, Odense, Denmark	Co-author
Prof. Dr.	Knut	Brockow	Germany	German Society of Dermatology (DDG)	Department of Dermatology and Allergy Biederstein, Faculty of Medicine, Technical University Munich, Munich, Germany	Co-author
Dr.	Zenon	Brzoza	Poland	Polish Society of Allergology (PTA)	Department of Internal Diseases with Division of Allergology, University of Opole, Opole, Poland	Co-author
Prof. Dr.	Herberto José	Chong-Neto	Brazil	Brazilian Society of Paediatrics (SBP)	Division of Allergy and Immunology, Department of Pediatrics, Federal University of Paraná, Curitiba, Brazil	Co-author
Prof. Dr.	Martin K.	Church	UK	Global Allergy and Asthma European Network (GA²LEN)	Charité-Universitätsmedizin Berlin, Germany, University of Southampton, UK	Co-author
Dr.	Paulo Ricardo	Criado	Brazil	Brazilian Society of Dermatology (SBD)	Sociedade Brasileira de Dermatologia (SBD), Centro Universitário FMABC, Alergoskin (UCARE), Brazil	Co-author

(Continues)

TABLE 1 (Continued)

Title	First name	Last name	Country	Nominating society	Affiliations	Role
Dr.	Inna Vladimirovna	Danilycheva	Russia	Russian Association of Allergology and Clinical Immunology (RAACI)	Department of Allergology and Immunotherapy, National Research Center-Institute of Immunology Federal Medical-Biological Agency of Russia, Moscow, Russia	Co-author
Dr.	Luis Felipe	Ensina	Brazil	Brazilian Association of Allergy and Immunology (ASBAI)	Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil	Co-author
Prof. Dr.	Luz	Fonacier	USA	American College of Allergy, Asthma and Immunology (ACAAI)	New York University Long Island School of Medicine, New York, USA	Co-author
Dr.	Krisztián	Gáspár	Hungary	Hungarian Dermatological Society (MDT)	Division of Dermatological Allergology, Department of Dermatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary	Co-author
Prof. Dr.	Aslı	Gelincik	Turkey	Turkish National Society of Allergy and Clinical Immunology (TNSACI)	Division of Immunology and Allergic Diseases, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey	Co-author
Prof. Dr.	Ana M.	Giménez-Arnau	Spain	Spanish Academy of Dermatology and Venereology (AEDV), European Academy of Allergy and Clinical Immunology (EAACI)	Department of Dermatology, Hospital del Mar, Institut Mar d'Investigacions Mèdiques, Universitat Autònoma y Universitat Pompeu Fabra, Barcelona, Spain	Co-author
Prof. Dr.	Kiran	Godse	India	Indian Association of Dermatologists, Venereologists and Leprologists (IADVL)	Department of Dermatology, D Y Patil University School of Medicine, Navi Mumbai, India	Co-author
Prof. Dr.	Margarida	Gonçalo	Portugal	Portuguese Society of Dermatology and Venereology (SPDV)	Department of Dermatology, Coimbra University Hospital and Faculty of Medicine, University of Coimbra, Coimbra, Portugal	Co-author
Dr.	Clive	Grattan	UK	British Society for Allergy and Clinical Immunology (BSACI), European Academy of Allergy and Clinical Immunology (EAACI)	St John's Institute of Dermatology, Guy's Hospital, London, UK	Co-author
Dr.	Martine	Grosber	Belgium	Royal Belgian Society of Dermatology and Venereology (RBSDV)	Department of Dermatology, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium	Co-author
Prof. Dr.	Eckard	Hamelmann	Germany	German Society of Allergology and Clinical Immunology (DGAKI)	Department of Pediatrics, Children's Center Bethel, University Hospital OWL, University Bielefeld, Bielefeld, Germany	Co-author
Dr.	Jacques	Hébert	Canada	Canadian Society of Allergy and Clinical Immunology (CSACI)	Service d'allergie, Centre Hospitalier Université Laval/ Centre Hospitalier Universitaire de Québec, Québec, QC, Canada	Co-author

TABLE 1 (Continued)

Title	First name	Last name	Country	Nominating society	Affiliations	Role
Prof. Dr.	Michihiro	Hide	Japan	Japanese Dermatological Association (JDA) and Japanese Society of Allergology (JSA)	Department of Dermatology, Hiroshima University, Hiroshima, Japan (Current affiliation: Department of Dermatology, Hiroshima Citizens Hospital, Hiroshima, Japan)	Co-author
Prof. Dr.	Allen	Kaplan	USA	World Allergy Organization (WAO)	Department of Medicine, Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Medical University of South Carolina, Charleston, SC, USA	Co-author
Prof. Dr.	Alexander	Kapp	Germany	Deutsche Akademie für Allergologie und Umweltmedizin (DAAU)	Department of Dermatology & Allergy, Hannover Medical School (MHH), Hannover, Germany	Co-author
Prof. Dr.	Aharon	Kessel	Israel	Israel Association of Allergy and Clinical Immunology (IAACI)	Division of Allergy and Clinical Immunology, Bnai Zion Medical Center and the Bruce and Ruth Rappaport Faculty of Medicine, Technion, Haifa, Israel	Co-author
Dr.	Emek	Kocatürk	Turkey	Turkish Society of Dermatology (TDD)	Department of Dermatology, Koç University School of Medicine, Istanbul, Turkey	Co-author
Prof. Dr.	Kanokvalai	Kulthanan	Thailand	Dermatological Society of Thailand (DST)	Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand	Co-author
Dr.	Désirée	Larenas-Linnemann	Mexico	Global Allergy and Asthma European Network (GA^2LEN)	Hospital Médica Sur, Mexico City, Mexico	Co-author
Prof. Dr.	Antti	Lauerma	Finland	Finnish Dermatological Society (FDS)	Department of Dermatology, Allergology and Venereology, University of Helsinki and Helsinki University Hospital, Inflammation Centre, Helsinki, Finland	Co-author
Dr.	Tabi Anika	Leslie	UK	British Association of Dermatologists (BAD)	Department of Dermatology, Royal Free Hospital, London, UK	Co-author
Prof. Dr.	Markus	Magerl	Germany	Urtikaria Netzwerk Berlin Brandenburg (UNBB)	Comprehensive Allergy Centre Charité, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany	Co-author
Dr.	Michael	Makris	Greece	Hellenic Society of Allergology and Clinical Immunology (EEAKA)	Allergy Unit, 2nd Department of Dermatology and Venereology, National and Kapodistrian University of Athens, University General Hospital "Attikon", Athens, Greece	Co-author

(Continues)

TABLE 1 (Continued)

Title	First name	Last name	Country	Nominating society	Affiliations	Role
Prof. Dr.	Marcus	Maurer	Germany	European Academy of Allergy and Clinical Immunology (EAACI)	Comprehensive Allergy Centre Charité, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany	Guideline co-coordinator, co-author
Prof. Dr.	Raisa Yakovlevna	Meshkova	Russia	Russian Association of Allergology and Clinical Immunology (RAACI)	Department of Clinical Immunology and Allergology, Smolensk State Medical University, Smolensk, Russia	Co-author
Prof. Dr.	Martin	Metz	Germany	European Mast Cell and Basophil Research Network (EMBRN)	Comprehensive Allergy Centre Charité, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany	Co-author
Dr.	Daniel	Micallef	Malta	Maltese Association of Dermatology & Venereology (MADV)	Department of Dermatology, Mater Dei Hospital, Msida, Malta	Co-author
Prof. Dr.	Charlotte G	Mortz	Denmark	European Academy of Allergy and Clinical Immunology (EAACI), Danish Society for Allergology (DSA)	Department of Dermatology and Allergy Centre, Odense Research Center for Anaphylaxis (ORCA), Odense University Hospital and University of Southern Denmark, Odense, Denmark	Co-author
Dr.	Hanneke	Oude-Elberink	Netherlands	Dutch Society of Allergology (NVvA)	University of Groningen, Groningen, The Netherlands	Co-author
Prof. Dr.	Ruby	Pawankar	India	Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI)	Department of Pediatrics, Nippon Medical School, Tokyo, Japan	Co-author
Prof. Dr.	Paolo	Pigatto	Italy	SIDeMaST, Italian Society of Medical, Surgical and Aesthetic Dermatology and Sexual Transmitted Diseases	Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy	Co-author
Prof. Dr.	Héctor	Ratti Sisa	Paraguay	Paraguayan Society of Immunology, Asthma and Allergy (SPAAI)	Primera Cátedra de Clínica Médica, Hospital de Clínicas de la Facultad de Ciencias Médicas-Universidad Nacional de Asunción, Asunción, Paraguay	Co-author
Dr.	María Isabel	Rojo Gutiérrez	Mexico	Mexican College of Clinical Immunology and Allergy (CMICA)	Hospital Juárez de México, Mexico City, Mexico	Co-author
Dr.	Sarbjit (Romi)	Saini	USA	Global Allergy and Asthma European Network (GA^2LEN), World Allergy Organization (WAO)	Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA	Co-author
Prof. Dr.	Peter	Schmid-Grendelmeier	Switzerland	Swiss Society of Dermatology and Venereology (SGDV)	Allergy Unit, Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland	Co-author
Prof. Dr.	Bulent Enis	Sekerel	Turkey	Turkish National Society of Allergy and Clinical Immunology (TNSACI)	Division of Pediatric Allergy and Asthma, Hacettepe University Faculty of Medicine, Ankara, Turkey	Co-author

TABLE 1 (Continued)

Title	First name	Last name	Country	Nominating society	Affiliations	Role
Dr.	Frank	Siebenhaar	Germany	European Mast Cell and Basophil Research Network (EMBRN)	Comprehensive Allergy Centre Charité, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany	Co-author
Dr.	Hanna	Siiskonen	Finland	Finnish Dermatological Society (FDS)	Department of Pathology, Diagnostic Imaging Centre, Kuopio University Hospital, Kuopio, Finland	Co-author
Prof. Dr.	Angèle	Soria	France	French Society of Dermatology (Groupe Urticaire de la Société francaise de dermatologie) (SFD)	Department of Dermatology and Allergology, Tenon Hospital, APHP Sorbonne University and Cimi-Paris Inserm 1135, Paris, France	Co-author
Prof. Dr.	Petra	Staubach-Renz	Germany	Urticaria network (patient organization) (UNEV)	Department of Dermatology, University Medical Center Mainz, Mainz, Germany	Co-author
Prof. Dr.	Luca	Stingeni	Italy	SIDeMaST, Italian Society of Medical, Surgical and Aesthetic Dermatology and Sexual Transmitted Diseases	Dermatology Section, Department of Medicine, University of Perugia, Perugia, Italy	Co-author
Dr.	Gordon	Sussman	Canada	Canadian Society of Allergy and Clinical Immunology (CSACI)	Division of Allergy and Clinical Immunology, St. Michael's Hospital and University of Toronto, Toronto, Canada	Co-author
Prof. Dr.	Andrea	Szegedi	Hungary	Hungarian Dermatological Society (MDT)	Division of Dermatological Allergology, Department of Dermatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary	Co-author
Prof. Dr.	Simon Francis	Thomsen	Denmark	Danish Dermatological Society (DDS)	Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark	Co-author
Prof. Dr.	Zahava	Vadasz	Israel	Israel Association of Allergy and Clinical Immunology (IAACI)	Proteomic and Clinical Flow Cytometry Unit, Bnai Zion Medical Center, Rappaport Faculty of Medicine, Technion, Haifa, Israel	Co-author
Dr.	Christian	Vestergaard	Denmark	Danish Dermatological Society (DDS)	Department of Dermatology and Venereology, Aarhus University Hospital, Aarhus, Denmark	Co-author
Prof. Dr.	Bettina	Wedi	Germany	German Society of Allergology and Clinical Immunology (DGAKI)	Department of Dermatology and Allergy, Comprehensive Allergy Center, Hannover Medical School, Hannover, Germany	Co-author
Prof. Dr.	Zuotao	Zhao	China	Chinese Dermatologist Association (CDA)	Department of Dermatology and Venereology, Peking University First Hospital, Beijing, China	Co-author
Prof. Dr.	Torsten	Zuberbier	Germany	European Dermatology Forum (EDF)	Comprehensive Allergy Centre Charité, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany	Guideline co-coordinator, co-author

The present update and revision of the guideline was undertaken by a panel of 64 urticaria experts from 31 countries, nominated as delegates by 50 participating national and/or international medical or scientific societies (Table 1). All of the societies involved endorse the guideline. The work of the expert panel was supported by a team of EuroGuiDerm methodologists led by Prof. Alexander Nast (Table 2) and included the contributions of the participants of the consensus conference.

The aim of the guideline is to provide a definition and classification of urticaria, thereby facilitating the interpretation of data from different centers and areas of the world regarding underlying causes, eliciting factors, comorbidities, burden to patients and society, and therapeutic responsiveness of subtypes of urticaria. Furthermore, the guideline provides recommendations for diagnostic and therapeutic approaches in common subtypes of urticaria. This is an international guideline and takes into consideration the global diversity of patients, physicians, medical systems and access to diagnosis and treatment.

2 | METHODS

The detailed methods used to develop this guideline are published as a separate Methods Report, which is available on the EDF website alongside a separate Evidence Report including all evidence-to-decision frameworks (https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html).

The guideline takes into account the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument[5] and the methods suggested by the GRADE working group. The literature review was conducted using the methods given in the Cochrane Handbook for Systematic Reviews of Interventions.[6]

In summary, experts from 50 societies were nominated to be involved in the development of this update and revision of the guideline. All members of the expert panel received an invitation to submit a declaration of their conflicts of interest (COIs) online and to self-declare their personal financial interests (P-F), non-personal financial interests (NP-F), and personal non-financial interests (P-NF). An overview of the declarations of P-F conflicts of interests is given in the Methods Report. Overall, 40 members of the expert panel (62.5%) declared that they had no P-F COIs.

For the 2021 update of the guideline, the same key questions were used as those developed for the version of the guideline published in 2018. Details on the processes used to develop these questions are available in the Methods Report of the latter.[7] The key questions were translated into the PICO format, which specifies the intervention, comparison and outcome used to assess efficacy and safety. Systematic searches for randomized controlled trials and clinical controlled trials were undertaken in three databases on 15 May 2020.

The search identified a total of 2053 records. Two independent reviewers evaluated the literature and extracted eligible data. The removal of duplicates and title/abstract screening left 144 records to be assessed as full texts for eligibility, of which 123 were excluded.

TABLE 2 Members of the EuroGuiDerm guideline methodology group

Title	First name	Last name	Country	Organization	Role
	Martin	Dittmann	Germany	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Information specialist, team support
Dr.	Corinna	Dressler	Germany	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist
	Matthew	Gaskins	Germany	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist
Prof. Dr.	Alexander	Nast	Germany	Division of Evidence-Based Medicine (dEBM), Charité – Universitätsmedizin Berlin	Methodologist, conference facilitator

TABLE 3 Summary of the GRADE approach to assessing the quality of evidence by outcome in randomized controlled trials[159]

Initial rating of quality of the body of evidence	Criteria that may decrease the quality rating	Criteria that may increase the quality rating	Quality of the body of evidence	
High	• Risk of bias • Inconsistency • Indirectness • Imprecision • Publication bias	• Large effect • Dose response • Residual confounding	High (++++)	We are very confident that the true effect lies close to that of the estimate of effect.
			Moderate (+++)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
			Low (++)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
			Very low (+)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

A total of 21 records were determined to fulfill the inclusion criteria. A graphical breakdown of this process and a list of excluded full-text publications with reasons for exclusion can be found in the separate Methods Report.

Wherever possible, we calculated effect measures with confidence intervals and performed meta-analyses using Review Manager.[8] We assessed the quality of the evidence following the GRADE approach using GRADEpro Guideline Development Tool (GDT).[9,10] Five criteria (risk of bias, inconsistency, indirectness, imprecision, and publication bias) were evaluated for each outcome resulting in an overall assessment of quality of evidence (Table 3). Effect measures such as risk ratios express the size of an effect, and the quality rating expresses how much confidence one can have in a result.

Subsequently, evidence-to-decision frameworks were created to help the expert panel make judgments for specific comparisons about the size of the desirable and undesirable effects, as well as the balance between these, and to provide an overview of the quality of the evidence. The evidence assessment yielded 14 new or updated GRADE evidence profiles and 14 new or updated evidence-to-decision frameworks. A summary of the evidence is given in the separate Evidence Report. Recommendations for each of the evidence-based key questions were subsequently drafted using standardized wording (Table 4).

Before the consensus conference, two rounds of pre-voting were held via an online survey to familiarize the expert panel with all of the draft recommendations and evidence-to-decision frameworks, gather their feedback on these, and subsequently use this feedback to modify the recommendations or to draft alternatives to them to be presented and voted upon during the consensus conference. All members of the expert panel were eligible for pre-voting (regardless of whether they had P-F conflicts of interests). Of 61 members of the expert panel, 50 completed the first survey (response rate 81.9%), which focused on the diagnosis and classification section of the guideline, and 60 completed the second survey (response rate 98.4%), which focused on the management section of the guideline. The results were fed back to the expert panel. All evidence-to-decision frameworks and draft recommendations were made available in advance to the participants of the consensus conference.

The consensus conference took place on 3 December 2020 and was held in a hybrid format. Participants consisted of the members of the expert panel and a broader group of up to 100 professionals comprising physicians regularly involved in treating patients with urticaria, basic or clinical researchers in the field, and representatives of patient organizations and advocacy groups. Voting took place online using the Slido© polling platform. To be able to vote, participants were required to have submitted a conflict of interest declaration. Everyone except for those employed at a pharmaceutical company was eligible to vote and received a code to access the live polls. During the conference, the nominal group technique was used to discuss, modify, and reach agreement on the different recommendations[11]: Each draft recommendation was presented alongside the relevant evidence or justification; this was followed by open discussion, preliminary voting or collection of suggestions for alternative wording, and then the final vote. Strong consensus was defined as 90% agreement or higher, and consensus as 70–89% agreement. All recommendations were voted on by at least 89 participants and were passed with at least 75% agreement.

After the conference, the text of the previous version of the guideline published in 2018 was amended by the guideline coordinators and the methodologist team in line with the results of the voting and the points discussed during the conference and the pre-conference rounds of online voting. The draft was subsequently reviewed internally by the expert panel and externally by the participating national and international societies.

In the guideline itself, the strength of the consensus reached for each recommendation is reported as shown in Table 5.

Each recommendation in the guideline is formatted as shown in Boxes 1–3. At the top of each box, the question of interest is given (eg, "Should we … in chronic urticaria?"). In the row below the question of interest, the recommendation is spelled out in full using the standardized wording and symbols shown in Table 4. In Box 1, for example, we can see that a strong recommendation is being made (ie, "We recommend…" and "↑↑" in dark green). Additionally, we can see, based on the information given on the right-hand side of this same row, that the eligible participants in the consensus conference agreed upon this recommendation and its wording with strong consensus (≥90% agreement) and that the recommendation is based on expert consensus. If the recommendation is based, additionally, on evidence from a systematic review of the literature, the phrase used here will read "Evidence- and consensus-based (see Evidence Report)" instead of "Expert consensus."

If there are multiple recommendations that address the same question of interest and each of these recommendations was voted upon separately, these can be grouped together as shown in Box 2. In this case, the strength of consensus and the evidence base are given for each recommendation separately.

In Box 3, we also see two recommendations instead of one. However, in this case, because these were voted on jointly in the consensus conference, the information on the strength of consensus and the evidence base are shown only once and apply to both recommendations.

3 | DEFINITION

3.1 | Definition

Urticaria is a condition characterized by the development of wheals (hives), angioedema, or both. Urticaria needs to be differentiated from other medical conditions where wheals, angioedema, or both

Definition

Urticaria is a condition characterized by the development of wheals (hives), angioedema or both.

TABLE 4 Standardized wording and symbols for guideline recommendations

Strength of recommendation	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	"We **recommend**…"	↑↑	We believe that all or almost all informed people would make a choice in favor of using this intervention. Clinicians will not have to spend as much time on the process of decision-making with the patient and may devote that time instead to overcoming barriers to implementation and adherence. In most clinical situations, the recommendation can be adopted as a policy.
Weak recommendation **for** the use of an intervention	"We **suggest**…"	↑	We believe that most informed people would make a choice in favor of using this intervention, but a substantial number would not. Clinicians and other healthcare providers will need to devote more time to the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making will require substantial debate.
No recommendation with respect to an intervention	"We **cannot make a recommendation** with respect to…"	0	Currently, a recommendation in favor of or against using this intervention cannot be made due to certain circumstances (eg, unclear or balanced benefit-risk ratio, no data available).
Weak recommendation **against** the use of an intervention	"We **suggest against**…"	↓	We believe that most informed people would make a choice against using this intervention, but a substantial number would not.
Strong recommendation **against** the use of an intervention	"We **recommend against**…"	↓↓	We believe that all or almost all informed people would make a choice against using this intervention. This recommendation can be adopted as a policy in most clinical situations.

TABLE 5 Definitions of strength of consensus

Strong consensus	Agreement of ≥90% participants
Consensus	Agreement of 70–89% participants
Agreement of the majority	Agreement of 51–69% participants

BOX 1 Format for individual guideline recommendations, including strength of consensus and evidence base

Should we … in chronic urticaria?

We **recommend** that … ↑↑ Strong consensus[1] / Expert consensus

[1] ≥90% agreement

BOX 2 Format for multiple guideline recommendations voted upon separately, including strength of consensus and evidence base for each

Should we … in chronic urticaria?

We **recommend** that … ↑↑ Strong consensus[1] / Expert consensus

[1] ≥90% agreement

We **suggest** that … ↑ Strong consensus[1] / Expert consensus

[1] ≥90% agreement

BOX 3 Format for multiple guideline recommendations voted on jointly, including strength of consensus and evidence base

Should we … in chronic urticaria?

We **recommend** that … / We **recommend** using … ↑↑ Strong consensus[1] / Expert consensus

[1] ≥90% agreement

can occur as features of a spectrum of clinical conditions, for example, anaphylaxis, autoinflammatory syndromes, urticarial vasculitis, or bradykinin-mediated angioedema including hereditary angioedema (HAE).

TABLE 6 Recommended classification of chronic urticaria

Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria (CSU)	**Inducible Urticaria**
Spontaneous appearance of wheals, angioedema, or both for >6 weeks due to known[a] or unknown causes.	Symptomatic dermographism[b] Cold urticaria[c] Delayed pressure urticaria[d] Solar urticaria Heat urticaria[e] Vibratory angioedema[f] Cholinergic urticaria Contact urticaria Aquagenic urticaria

Note: Chronic urticaria (CU) is classified as spontaneous (CSU) and inducible (CIndU). CSU comes as CSU with known cause and CSU with unknown cause. CIndU is further subclassified as symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, and vibratory angioedema (collectively referred to as chronic physical urticaria), as well as cholinergic urticaria, contact urticaria, and aquagenic urticaria. CU patients can have more than one form of CU including more than one form of CIndU and they often do.

Table is based on expert consensus and achieved ≥90% agreement in the consensus conference.

[a]For example, type I autoimmunity (autoallergy) and type IIb autoimmunity, with mast cell–activating autoantibodies

[b]Formerly called *urticaria factitia* or dermographic urticaria.

[c]Also called cold contact urticaria.

[d]Also called pressure urticaria.

[e]Also called heat contact urticaria.

[f]Also called Vibratory angioedema/urticaria.

A A wheal has three typical features:
1. a sharply circumscribed superficial central swelling of variable size and shape, almost invariably surrounded by reflex erythema,
2. an itching or sometimes burning sensation,
3. a fleeting nature, with the skin returning to its normal appearance, usually within 30 min to 24 h.

B Angioedema is characterized by
1. a sudden, pronounced erythematous or skin-colored deep swelling in the lower dermis and subcutis or mucous membranes,
2. tingling, burning, tightness, and sometimes pain rather than itch,
3. a resolution slower than that of wheals (can take up to 72 h).

3.2 | Classification of urticaria on the basis of its duration and the relevance of eliciting factors

The spectrum of clinical manifestations of different urticaria types and subtypes is very wide. Additionally, two or more different subtypes of urticaria can coexist in any given patient.

Urticaria is classified based on its duration, as acute or chronic, and the role of definite triggers, as inducible or spontaneous. Acute urticaria is defined as the occurrence of wheals, angioedema, or both for 6 weeks or less. Chronic urticaria is defined as the occurrence of wheals, angioedema, or both for more than 6 weeks. Chronic urticaria can come with daily or almost daily signs and symptoms or an intermittent/recurrent course. CSU may recur after a months or years of full remission.

Inducible urticaria is characterized by definite and subtype-specific triggers of the development of wheals, angioedema, or both. These triggers are definite because wheals, angioedema, or both always and never occur when the trigger is present and absent, respectively. These triggers are specific because each subtype of inducible urticaria has its relevant trigger, for example cold in cold urticaria, and this trigger is not relevant in other forms of inducible urticaria. Rare subtypes of inducible urticaria exist in which the combined presence of two or more definite and specific triggers is required for the induction of wheals, angioedema, or both, for example cold-induced cholinergic urticaria.[12]

Some patients with spontaneous urticaria experience trigger-induced wheals, angioedema, or both. These triggers are not definite, as their presence does not always induce signs and symptoms and because wheals, angioedema, or both also occur without them, that is, spontaneously. Some patients can present with more than one subtype of urticaria, which can also respond independently to treatment.

TABLE 7 Differential diagnoses of urticaria

Maculopapular cutaneous mastocytosis (urticaria pigmentosa) and indolent systemic mastocytosis with involvement of the skin
Mast cell activation syndrome (MCAS)
Urticarial vasculitis
Bradykinin-mediated angioedema (eg, HAE)
Exercise-induced anaphylaxis
Cryopyrin-associated periodic syndromes (CAPS; urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue, and headaches), that is, Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), or Neonatal Onset Multisystem Inflammatory Disease (NOMID).
Schnitzler's syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy)
Gleich's syndrome (episodic angioedema with eosinophilia)
Well's syndrome (granulomatous dermatitis with eosinophilia/eosinophilic cellulitis)
Bullous pemphigoid (prebullous stage)
Adult-onset Still's disease (AOSD)

Note: These diseases and syndromes are related to urticaria 1) because they can present with wheals, angioedema, or both and/or 2) because of historical reasons. They are differential diagnoses of urticaria.

How should urticaria be classified?

We **recommend** that urticaria is classified based on its duration as acute (≤6 weeks) or chronic (>6 weeks).	↑↑	Strong consensus[1] Expert consensus

[1]≥90% agreement

We **recommend** that urticaria is classified as spontaneous (no definite eliciting factor involved) or inducible (specific definite factor involved).	↑↑	Strong consensus[1] Expert consensus

[1]≥90% agreement

Table 6 shows the classification of chronic urticaria (CU) subtypes for clinical use. This classification has been maintained from the previous version of the guideline by strong consensus (≥90%).

Should we maintain the current guideline classification of chronic urticaria?

We **recommend** that the current guideline classification of chronic urticaria should be maintained.	↑↑	Strong consensus[1] Expert consensus

[1]≥90% agreement

Urticarial vasculitis, maculo-papular cutaneous mastocytosis (formerly called urticaria pigmentosa) and indolent systemic mastocytosis with involvement of the skin, mast cell activation syndrome (MCAS), autoinflammatory syndromes (eg, cryopyrin-associated periodic syndromes or Schnitzler's syndrome), non-mast cell mediator-mediated angioedema (eg, bradykinin-mediated angioedema), and other diseases and syndromes that can manifest with wheals and/or angioedema are not considered to be types of urticaria, due to their distinctly different pathophysiologic mechanisms and/or clinical presentation (Table 7).

3.3 | Pathophysiological aspects

Urticaria is a predominantly mast cell–driven disease.[13] Histamine and other mediators, such as platelet-activating factor (PAF) and cytokines released from activated skin mast cells, result in sensory nerve activation, vasodilatation and plasma extravasation as well as cell recruitment to urticarial lesions. The mast cell–activating signals in urticaria are heterogeneous, diverse, and include T cell–driven cytokines and autoantibodies. Histologically, wheals are characterized by edema of the upper and mid dermis, with dilatation and augmented permeability of the postcapillary venules as well as lymphatic vessels of the upper dermis. In angioedema, similar changes occur primarily in the lower dermis and the subcutis. Skin affected by wheals shows a mixed inflammatory perivascular infiltrate of variable intensity, consisting of T cells, eosinophils, basophils, and other cells. Vessel-wall necrosis, a hallmark of urticarial vasculitis, does not occur in urticaria.[14-18] The nonlesional skin of chronic spontaneous urticaria (CSU) patients shows upregulation of adhesion molecules, infiltrating eosinophils, altered cytokine expression[19] and sometimes a mild-to-moderate increase of mast cell numbers.[13] These findings underline the complex nature of the pathogenesis of urticaria, which has many features in addition to the release of histamine from dermal mast cells.[20–22] Some of these features of urticaria are also seen in a wide variety of inflammatory conditions and are thus not specific or of diagnostic value. A search for more specific histological biomarkers for different subtypes of urticaria and for distinguishing urticaria from other conditions is desirable.[23]

3.4 | Burden of disease

The burden of CU for patients, their family and friends, the healthcare system and society is substantial.[24] The use of patient-reported outcome measures such as the urticaria activity score (UAS), the angioedema activity score (AAS), the CU quality of life questionnaire (CU-Q2oL), the angioedema quality of life questionnaire (AE-QoL), the urticaria control test (UCT), and the angioedema control test (AECT) in studies and clinical practice has helped to better define the effects and impact of CU on patients.[25] The available data indicate that urticaria markedly affects both objective functioning and subjective well-being.[26–28] Previously, O'Donnell et al. showed that health status scores in CSU patients are comparable to those reported by patients with coronary artery disease.[29] Furthermore, both health status and subjective satisfaction in patients with CSU are lower than in healthy subjects and in patients with respiratory allergy.[30] CU also comes with considerable costs for patients and society.[31–33]

4 | DIAGNOSIS OF URTICARIA

Detailed history taking is essential in urticaria; it is the first step in the diagnostic workup of all urticaria patients. The second step is the physical examination of the patient. As wheals and angioedema are transient and may not be present at the time of physical examination, it is important to review patients' documentation of signs and symptoms (including pictures of wheals and/or angioedema). The third step, in chronic urticaria, is a basic diagnostic workup, with limited tests (see Table 8; recommended routine diagnostic tests). Further individually selected diagnostic tests may be useful, based on the outcome of the first three steps and depending on the urticaria type and subtype (Table 8; extended diagnostic program). The aims of all diagnostic tests performed should be clear to the physician and patient.

4.1 | Diagnostic workup in acute urticaria

Acute urticaria, because it is self-limiting, usually does not require a diagnostic workup apart from anamnesis for possible trigger factors. The only exception is the suspicion of acute urticaria due to a type I food allergy in sensitized patients or drug hypersensitivity, especially for non-steroidal anti-inflammatory drugs (NSAIDs). In this case, allergy tests and patient education may be useful to allow patients to avoid re-exposure to relevant causative factors.

TABLE 8 Recommended diagnostic tests in frequent urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme[a] (based on history) – For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None[b]
	CSU	Differential blood count. ESR and/or CRP IgG anti-TPO and total IgE[e]	Avoidance of suspected triggers (eg, drugs); diagnostic tests for (in no preferred order): (i) infectious diseases (eg, *Helicobacter pylori*); (ii) functional autoantibodies (eg, basophil test); (iii) thyroid gland disorders (thyroid hormones and autoantibodies); (iv) allergy (skin tests and/or allergen avoidance test, eg, avoidance diet); (v) concomitant CIndU, see below[45];(vi) severe systemic diseases (eg, tryptase); and (vii) other (eg, lesional skin biopsy)
Inducible urticaria	Cold urticaria	Cold provocation and threshold test[c,d]	Differential blood count and ESR or CRP, rule out other diseases, especially infections[160]
	Delayed pressure urticaria	Pressure test and threshold test[c,d]	None
	Heat urticaria	Heat provocation and threshold test[c,d]	None
	Solar urticaria	UV and visible light of different wavelengths and threshold test[c]	Rule out other light-induced dermatoses
	Symptomatic dermographism		
	Elicit dermographism and threshold test[c,d]	Differential blood count, ESR or CRP	
	Vibratory angioedema	Test with vibration, for example, Vortex-mixer[d]	None
	Aquagenic urticaria	Provocation testing[d]	None
	Cholinergic urticaria	Provocation and threshold testing[d]	None
	Contact urticaria	Provocation testing[d]	None

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

[a]Depending on suspected cause.

[b]Unless strongly suggested by patient history, for example, allergy.

[c]All tests are done with different levels of the potential trigger to determine the threshold.

[d]For details on provocation and threshold testing see[45]

[e]For patients in specialist care

Should routine diagnostic measures be performed in acute urticaria?

We **recommend against** any routine diagnostic measures in acute spontaneous urticaria.

Strong consensus[1]

Expert consensus

[1]≥90% agreement

4.2 | Diagnostic workup in CSU

In CSU, the diagnostic workup has seven major aims. They are to confirm the diagnosis and exclude differential diagnoses; to look for the underlying causes; to identify relevant conditions that modify disease activity; to check for comorbidities; to identify the consequences of CSU; to assess predictors of the course of disease and response to treatment; and to monitor disease activity, impact, and control (Table 9).[34]

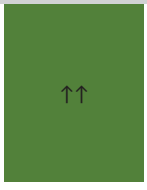
In all CSU patients, the diagnostic workup includes a thorough history, physical examination (including review of pictures of wheals and/or angioedema), basic tests, and the assessment of disease activity, impact, and control. The basic tests include a differential blood count and CRP and/or ESR, in all patients, and total IgE and IG-anti-TPO, in patients in specialist care. Based on the results obtained by these measures, further diagnostic testing may be performed as indicated.

4.2.1 | Confirmation of CSU and exclusion of differential diagnoses

Wheals or angioedema also occur in patients with diseases other than CSU (Figure 1). In patients who exclusively develop wheals (but not angioedema), urticarial vasculitis and autoinflammatory disorders such as Schnitzler syndrome or cryopyrin-associated periodic syndromes (CAPS) need to be ruled out. On the contrary, in patients who suffer exclusively from recurrent angioedema (but not from wheals), bradykinin-mediated angioedema-like angiotensin-converting-enzyme (ACE)-inhibitor-induced angioedema and HAE should be considered as differential diagnoses (Figure 1). The assessment of patients for differential diagnoses of CSU is guided by the history (Figure 1) and supported by basic tests, for example, CRP and/or ESR, differential blood count. Further testing should be performed only as indicated by the results of the history, physical examination, and basic testing.

Should differential diagnoses be considered in patients with chronic spontaneous urticaria?

We **recommend** that differential diagnoses be considered in all patients with signs or symptoms suggestive of chronic urticaria based on the guideline algorithm.



Strong consensus[1]

Expert consensus

[1] 100% agreement

TABLE 9 The aims of the diagnostic workup in patients with CSU[34]

What to do in every CSU patient			
History	Physical examination[a]	Basic tests[b]	UCT
Confirm	Rule out differential diagnoses		
Cause	Look for indicators of CSU^{aiTI}, CSU^{aiTIIb}		
Cofactors	Identify potential triggers, aggravators		
Comorbidities	For example, check for CIndU, autoimmunity, mental health		
Consequences	For example, identify problems with sleep, distress, sexual health, work, social performance		
Components	Assess potential biomarkers or predictors of treatment response		
Course	Monitor CSU activity, impact, and control		

Abbreviations: CSU, chronic spontaneous urticaria; CSU^{aiTI}, Type I autoimmune (autoallergic) CSU; CSU^{aiTIIb}, Type IIb autoimmune CSU; UCT, urticaria control test.

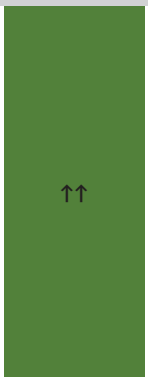
[a]Including review of patient photo documentation.

[b]Differential blood count, CRP/Erythrocyte sedimentation rate; IgG-anti-TPO, total IgE for patients in specialist care.

What routine diagnostic measures should be performed in chronic spontaneous urticaria?

We **recommend** limited investigations. Basic tests include differential blood count, CRP and/or ESR, and in specialized care total IgE and IgG anti-TPO, and more biomarkers as appropriate.

We **recommend** performing further diagnostic measures based on the patient history and examination, especially in patients with long-standing and/or uncontrolled disease.



Consensus[1]

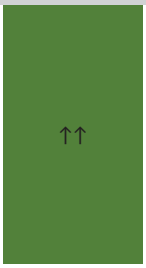
Expert consensus

[1]>75% agreement

Should routine diagnostic measures be performed in inducible urticaria?

We **recommend** using provocation testing to diagnose chronic inducible urticaria.

We **recommend** using provocation threshold measurements and the UCT to measure disease activity and control in patients with chronic inducible urticaria, respectively.



Strong consensus[1]

Expert consensus

[1] ≥90% agreement

4.2.2 | Identification of underlying causes

Although the pathogenesis of CSU is not yet fully understood, it is well established that its signs and symptoms are due to the

activation of skin mast cells and the subsequent release and effects of their mediators.[13] Based on recent evidence, it is known that the causes of CSU include autoimmunity Type I (CSU^{aiTI}, or "autoallergic CSU"; with IgE autoantibodies to self-antigens) and autoimmunity Type IIb (CSU^{aiTIIb}; with mast cell–directed activating autoantibodies). In CSU due to unknown cause (CSU^{uc}), as of yet unknown mechanisms are relevant for the degranulation of skin MC. The history and physical examination can provide clues on underlying causes. The results of the basic tests performed in CSU can point to CSU^{aiTI} vs CSU^{aiTIIb}, with CRP more often elevated and eosinophil and basophil levels more often reduced in CSU^{aiTIIb}. Testing for IgG-anti-TPO and total IgE, basic tests that should be performed in CSU patients in specialist care, can help to bring more clarity. CSU^{aiTIIb} patients are more likely to have low or very low total IgE and elevated levels of IgG-anti-TPO IgG, and a high ratio of IgG-anti-TPO to total IgE is currently the best surrogate marker for CSU^{aiTIIb}. More advanced tests, such as basophil activation testing for CSU^{aiTIIb}, can bring more clarity, and should be guided by and based on the history, physical examination, and results of basic testing. Other underlying causes include active thyroid disease, infections, inflammatory processes, food, and drugs but these can be both cause as well as only aggravating factor and are covered below. Intensive and costly general screening programs for causes of urticaria are advised against.

Importantly, there may be considerable variations in the frequency of underlying causes in different parts of the world, and regional differences are not well researched and understood.

4.2.3 | Identification of relevant conditions that modify disease activity

Identifying relevant conditions that modify CSU disease activity and factors that exacerbate CSU, such as drugs, food, stress, and infections, can help physicians and patients understand and sometimes change the course of CSU.

Drugs can trigger CSU exacerbation. NSAIDs are the most common drugs to do so, in up to one of four patients with the exception of paracetamol and/or COX-2 inhibitors as safer options in patients with CSU. Physicians should therefore ask patients about the intake of NSAIDs, including on demand use, and advise them that avoiding certain NSAIDs can prevent exacerbation. Provocation testing is usually not useful.

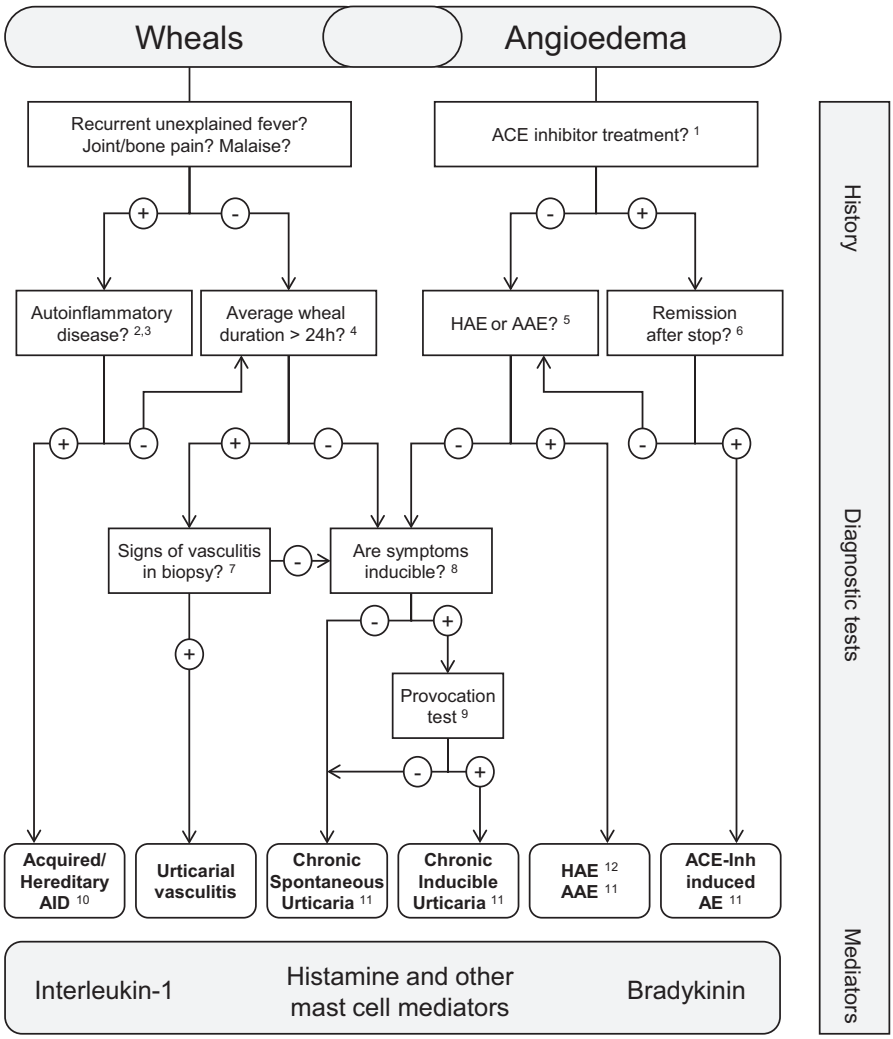


FIGURE 1 Diagnostic algorithm for patients presenting with wheals and/or angioedema for longer than 6 weeks AAE: Acquired angioedema due to C1-inhibitor deficiency; ACE-Inh: angiotensin converting enzyme inhibitor; AE: angioedema; AID: Auto-inflammatory disease; HAE: Hereditary angioedema

1 Apart from ACE inhibitors, angiotensin II type 1 receptor blockers (sartans), dipeptidyl peptidase IV inhibitors (gliptins) and neprilysin inhibitors have been described to induce angioedema but much less frequently

2 Patients should be asked for a detailed family history and age of disease onset

3 Test for elevated inflammation markers (C-reactive protein, erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis for hereditary periodic fever syndromes (e.g. Cryopyrin-associated periodic syndrome), if strongly suspected.

4 Patients should be asked: "For how long does each individual wheal last?"

5 Test for Complement C4, C1-INH levels and function; in addition test for C1q and C1-INH antibodies, if AAE is suspected; do gene mutation analysis, if former tests are unremarkable but patient's history suggests hereditary angioedema.

6 Remission should occur within a few days, in rare cases up to 6 months of ACE-inhibitor discontinuation.

7 Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of urticarial vasculitis?

8 Patients should be asked: "Can you make your wheals appear? Can you bring out your wheals?"

9 In patients with a history suggestive of inducible urticaria standardized provocation testing according to international consensus recommendations 45 should be performed.

10 Acquired autoinflammatory syndromes include Schnitzler's syndrome as well as systemic-onset juvenileidiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD); hereditary autoinflammatory syndromes include Cryopyrin-associated periodic syndromes (CAPS) such as familial cold auto-inflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID), more rarely hyper-IgD syndrome (HIDS) and tumor necrosis factor receptor alpha-associated periodic syndrome (TRAPS).

11 In some rare cases recurrent angioedema is neither mast cell mediator-mediated nor bradykinin-mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as "idiopathic angioedema" by some authors.

12 Several subtypes HAE are known: HAE-1: Hereditary angioedema due to C1-Inhibitor deficiency; HAE-2: Hereditary angioedema due to C1-Inhibitor dysfunction; HAE nC1-INH: Hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in FXII (factor 12), ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 (kininogen), MYOF (myoferlin), and HS3ST6 (heparan sulfate-glucosamine 3-Osulfotransferase 6) or unknown.

Food can trigger CSU exacerbation, and physicians should ask patients about this. Based on their answer, pseudoallergen- and histamine-low diets may be considered as an additional, individual diagnostic measure. Diagnostic diets should be maintained only for a limited time to avoid side effects and safety risks; 3–4 weeks are usually recommended. Importantly, diagnostic diets should not delay effective treatment.[35]

Stress can exacerbate CSU, and up to one third of CSU patients, see stress as an aggravating factor of their disease. Physicians should ask patients about the impact of stress on their disease and make them aware that stress reduction can be helpful.

4.2.4 | Identification of comorbidities and consequences of CSU

In CSU, the most common comorbidities are CIndUs, autoimmune diseases, and allergies.

Mental disorders, that is, depression and anxiety, sexual dysfunction, and sleep disturbance are common consequences.

Findings from the patient's medical history, physical examination, or basic testing that point to a comorbidity or consequence of CSU should prompt further investigations, for example screening for specific diseases by questionnaires, provocation tests, further laboratory tests or referral to a specialist.

4.2.5 | Identification of predictors of the course of disease and response to treatment

In CSU, disease duration, disease activity, and response to treatment are linked to clinical characteristics and laboratory markers. While none of these are definite predictors, they can help physicians to counsel their patients on the severity and expected duration of their disease and on what to expect from treatment. Concomitant CIndU, high disease activity, elevated CRP, and/or the presence of angioedema, for example, point to long duration of CSU and poor response to antihistamine treatment.[24,36,37]

4.2.6 | Assessment of disease activity, impact, and control

Patients should be assessed for disease activity, impact, and control at the first and every follow-up visit. Validated patient-reported outcome measures (PROMs) such as the urticaria activity score

TABLE 10 The urticaria activity score (UAS) and Angioedema Activity Score (AAS) for assessing disease activity in CSU

Urticaria activity score (UAS)		
Score	**Wheals**	**Pruritus**
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20–50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)
Angioedema Activity Score (AAS)		
Score	**Dimension**	**Answer options**
–	Have you had a swelling episode in the last 24 h?	No, yes
0–3	At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	Midnight–8 a.m., 8 a.m.–4 p.m., 4 p.m.–midnight
0–3	How severe is / was the physical discomfort caused by this swelling episode(s) (eg, pain, burning, itching?)	No discomfort, slight discomfort, moderate discomfort, severe discomfort
0–3	Are / were you able to perform your daily activities during this swelling episode(s)?	No restriction, slight restriction, severe restriction, no activities possible
0–3	Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	No, slightly, moderately, severely
0–3	How would you rate the overall severity of this swelling episode?	Negligible, mild, moderate, severe

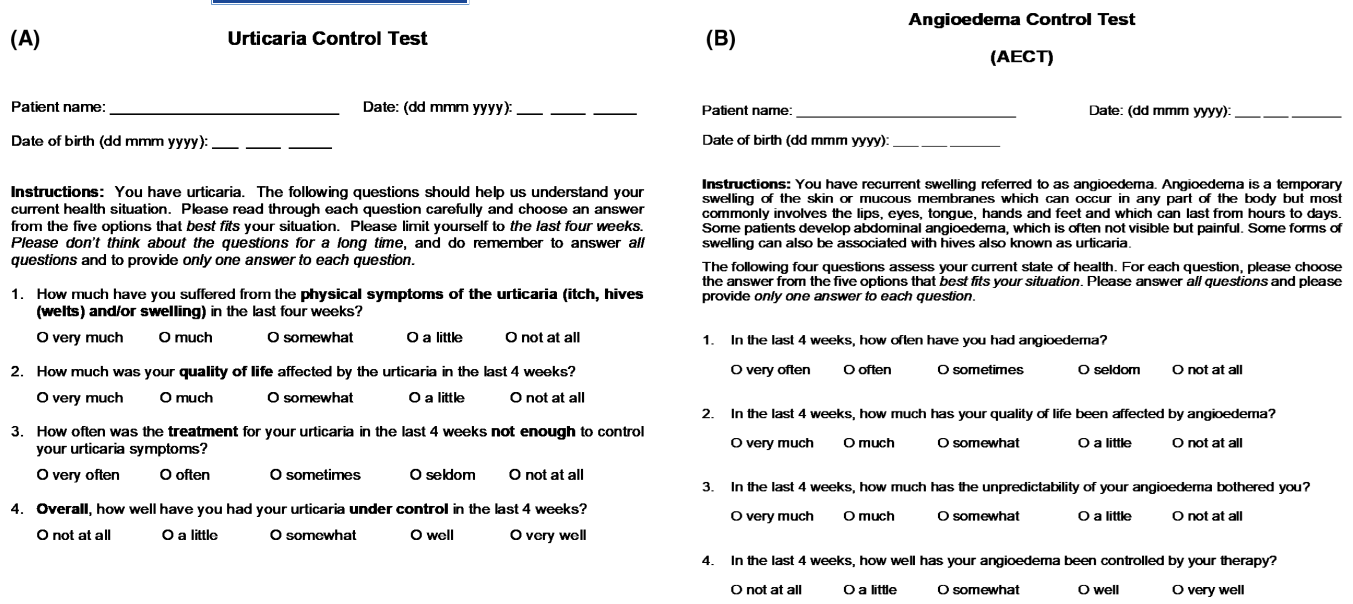
Note: For the UAS7, the sum of the score (0–3 for wheals +0–3 for pruritis) for each day is summarized over one week (7 days) for a maximum of 42. For the AAS, scores are summed up to an AAS day sum score (0–15), 7 AAS day sum scores to an AAS week sum score (AAS7, 0–105), and 4 ASS week sum scores may be summed up to an AAS 4-week sum score (AAS28, 0–420). Copyright for UAS: GA²LEN; copyright for AAS (UK version): MOXIE GmbH (www.moxie-gmbh.de).

(UAS, and the weekly urticaria activity score, that is, UAS7, calculated from it), the angioedema activity score (AAS), the chronic urticaria quality of life questionnaire (CU-Q2oL), the angioedema quality of life questionnaire (AE-QoL), the urticaria control test (UCT), and the angioedema control test (AECT) should be used for this purpose.[38,39] PROMs are available in a wide range of languages.

In CSU patients who develop wheals, disease activity should be assessed both in clinical care and trials with the UAS7 (Table 10), a unified and simple scoring system that was proposed in the last version of the guideline and has been validated.[40,41] The UAS7 is based on the assessment of key urticaria signs and symptoms (wheals and pruritus), which are documented by the patient, making this score especially valuable. The use of the UAS7 facilitates comparison of study results from different centers. As urticaria activity frequently changes, the overall disease activity is best measured by advising patients to document 24h self-evaluation scores once daily for several days. The UAS7, that is, the sum score of 7 consecutive days, should be used in routine clinical practice to determine disease activity and response to treatment of patients with CSU. For CSU patients who develop angioedema, with or without wheals, the Angioedema Activity Score (AAS) should be used to assess disease activity (Table 10).[42] CSU patients who experience wheals and angioedema should use the UAS7 and the AAS in combination.

In addition to disease activity, it is important to assess the impact of disease on quality of life as well as disease control both in clinical practice and trials. The CU-Q2oL should be used to determine QoL impairment in CSU patients with wheals. For CSU patients with angioedema, with or without wheals, the AE-QoL should be used. In CSU patients with wheals and angioedema, the CU-Q2oL and the AE-QoL should be used.

It is also important to assess disease control in patients with CSU. The urticaria control test (UCT) should be used to do this in CSU patients who develop wheals, with or without angioedema (Figure 2A). For CSU patients who develop angioedema, with or without wheals, the angioedema control test (AECT) should be used (Figure 2B). In CSU patients who develop wheals and angioedema, both the UCT and the AECT should be used. The UCT was developed and validated to determine the level of disease control in all forms of CU (CSU and CIndU).[43,44] The UCT is a simple four-item tool with a clearly defined cutoff for patients with "well-controlled" vs. "poorly controlled" disease, and it is thus suited for the management of patients in routine clinical practice. Its recall period is 4 weeks. A 7 days recall period UCT version is also available (UCT7). The UCT cutoff value for well-controlled disease is 12 out of 16 possible points. The AECT quantifies disease control in CSU patients with angioedema and patients with other forms of recurrent angioedema.[38] Like the UCT, the AECT is a retrospective PROM. Two versions exist, one with a 4-week recall period and one with a 3-month recall period. The AECT consists, like the UCT, of only four questions. Its cutoff for



(A)

Urticaria Control Test

Patient name: _____ Date: (dd mmm yyyy): ___ ___ _____

Date of birth (dd mmm yyyy): ___ ___ _____

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to *the last four weeks. Please don't think about the questions for a long time*, and do remember to answer *all questions* and to provide *only one answer to each question*.

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?
   O very much O much O somewhat O a little O not at all
2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?
   O very much O much O somewhat O a little O not at all
3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?
   O very often O often O sometimes O seldom O not at all
4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?
   O not at all O a little O somewhat O well O very well

(B)

Angioedema Control Test

(AECT)

Patient name: _____ Date: (dd mmm yyyy): ___ ___ _____

Date of birth (dd mmm yyyy): ___ ___ _____

Instructions: You have recurrent swelling referred to as angioedema. Angioedema is a temporary swelling of the skin or mucous membranes which can occur in any part of the body but most commonly involves the lips, eyes, tongue, hands and feet and which can last from hours to days. Some patients develop abdominal angioedema, which is often not visible but painful. Some forms of swelling can also be associated with hives also known as urticaria.

The following four questions assess your current state of health. For each question, please choose the answer from the five options that *best fits your situation*. Please answer *all questions* and please provide *only one answer to each question*.

1. In the last 4 weeks, how often have you had angioedema?
   O very often O often O sometimes O seldom O not at all
2. In the last 4 weeks, how much has your quality of life been affected by angioedema?
   O very much O much O somewhat O a little O not at all
3. In the last 4 weeks, how much has the unpredictability of your angioedema bothered you?
   O very much O much O somewhat O a little O not at all
4. In the last 4 weeks, how well has your angioedema been controlled by your therapy?
   O not at all O a little O somewhat O well O very well

FIGURE 2 A: The urticaria control test (UCT) and B: the angioedema control test (AECT). Copyright for both tools: MOXIE GmbH, Berlin, Germany (www.moxie-gmbh.de)

well-controlled disease is 10 points. Both the UCT and the AECT are easy to administer, complete, and score, and can help to guide treatment decisions.

Should patients with chronic urticaria be assessed for disease activity, impact, and control?

We **recommend** that patients with CU be assessed for disease activity, impact, and control at every visit.

↑↑

Strong consensus[1]

Expert consensus

[1]≥90% agreement

Which instruments should be used to assess and monitor disease activity in chronic spontaneous urticaria patients?

We **recommend** the use of the urticaria activity score, UAS7, and/or of the angioedema activity score, AAS, for assessing disease activity in patients with chronic spontaneous urticaria.

↑↑

Strong consensus[1]

Expert consensus

[1]≥90% agreement

Which instruments should be used to assess and monitor quality of life impairment in chronic spontaneous urticaria patients?

We **recommend** the use of the chronic urticaria quality of life questionnaire, CU-Q2oL, and the angioedema quality of life questionnaire, AE-QoL, for assessing quality of life impairment in patients with chronic spontaneous urticaria.

↑↑

Strong consensus[1]

Expert consensus

[1]≥90% agreement

Which instruments should be used to assess and monitor disease control in chronic spontaneous urticaria patients?

We **recommend** the use of the urticaria control test, UCT, and/or the angioedema control test, AECT, for assessing disease control in patients with CSU.

↑↑

Strong consensus[1]

Expert consensus

[1]≥90% agreement

4.3 | The diagnostic workup in CIndU

In patients with CIndU, the routine diagnostic workup should follow the consensus recommendations on the definition, diagnostic testing, and management of CindUs.[45] Diagnostics in CIndU aim to exclude differential diagnoses, to identify the subtype of CIndU, and to determine trigger thresholds.[45] The last of these is important as it allows for assessing disease activity and response to treatment.

For most CIndU subtypes, validated tools for provocation testing are available.[45] Examples include cold and heat urticaria, where a Peltier element-based provocation device (Temp*Test*®) is available,[46] symptomatic dermographism for which dermographometers (Dermographic Tester, FricTest) have been developed,[47,48] and delayed pressure urticaria (Dermographic Tester). In cholinergic urticaria, a graded provocation test with office-based methods, for example, pulse-controlled ergometry, is available.[49,50] Patients with contact urticaria or aquagenic urticaria should be assessed by appropriate cutaneous provocation tests.[45]

Disease control, in patients with CIndU, is assessed by provocation threshold testing and use of the UCT and AECT. Patient-reported outcome measures for disease activity and impact are available or being developed for some CindUs.[50,51]

4.4 | Diagnosis in children

Urticaria can occur in all age groups, including infants and young children. Recent reports indicate that, in children, the prevalence of CIndUs and CSU, disease characteristics, underlying causes of CSU, and response to treatment are very similar to those in adults.[52–59]

The diagnostic workup of CSU in children has the same aims as in adults. Differential diagnoses should be excluded with a special focus on cryopyrin-associated periodic syndrome (CAPS). CAPS is a rare disease with a urticaria-like rash that manifests in childhood.[60] If possible, that is, depending on the age of the child, disease activity, impact, and control should be assessed using assessment tools similar to those used in adults, although it has to be noted that no validated disease-specific tools for children are available as of now. Triggers of exacerbation should be identified and, where indicated, underlying causes, which appear to be similar to those in adults, should be searched for. In children with CIndU, similar tests for provocation and the determination of trigger thresholds should be performed (insofar as this is possible in terms of age-related cooperation).

5 | MANAGEMENT OF URTICARIA

5.1 | Basic considerations

1. The goal of treatment is to treat the disease until it is gone and as efficiently and safely as possible aiming at a continuous UAS7 = 0, complete control and a normalization of quality of life.
2. The therapeutic approach to CU should involve
   a. the search for and, if possible, elimination of underlying causes, which means healing the disease
   b. the avoidance of eliciting factors, reducing disease activity
   c. tolerance induction, reducing disease activity
   d. the use of pharmacological treatment to prevent mast cell mediator release and/or the effects of mast cell mediators, reducing disease activity
3. Treatment should follow the basic principles of treating as much as needed and as little as possible taking into consideration that the activity of the disease may vary. This implies stepping up or stepping down in the treatment algorithm according to the course of disease following the principle assess, adjust, act, and reassess (Figure 3). It is important to highlight that patients need good counseling regarding continuous treatment and using patient-reported outcome measures (PROMs), especially UAS.

Should treatment aim at complete symptom control in urticaria?

We **recommend** aiming at complete symptom control in urticaria, considering as much as possible the safety and the quality of life of each individual patient.

↑↑

Strong consensus[1]

Expert consensus

[1]≥90% agreement

5.2 | Identification and elimination of underlying causes and avoidance of eliciting factors

Although desirable, the elimination of underlying causes is not possible in most patients with urticaria. The underlying causes of CIndU are unknown, the underlying causes of acute spontaneous urticaria remain unknown in most patients, and the most common underlying causes of CSU, type I and type IIb autoimmunity, cannot be eliminated. The reduction of autoantibodies by plasmapheresis has been shown to be of temporary benefit in some, severely affected patients with CSU,[61] but experience and evidence are limited and costs are high.

In contrast, the avoidance of triggering factors, where possible, can be of benefit for patients with urticaria.[62] In CIndU, avoidance of specific and definite triggers for the development of signs and symptoms, for example, cold in cold urticaria, can reduce disease activity. In CSU, avoidance of individually relevant and unspecific triggers, for example stress or the intake of NSAIDs, can help to reduce disease exacerbations. Importantly, the avoidance of triggers, in patients with CIndU and in patients with CSU, can result in markedly impaired quality of life, for example in patients with cholinergic urticaria who abstain from physical exercise or in patients with solar urticaria who avoid being outside.

5.2.1 | Drugs

When these agents are suspected in the course of diagnostic workup, they should be omitted entirely or substituted by another class of agents if indispensable. Drugs causing non-allergic hypersensitivity reactions (the prototypes being NSAIDs) cannot only elicit, but can also aggravate preexisting CSU, so that elimination in the latter case will only improve symptoms in some patients.

Should patients with chronic spontaneous urticaria be advised to discontinue medication that is suspected to worsen the disease?

We **recommend** advising patients with chronic spontaneous urticaria to discontinue medication that is suspected to worsen the disease, for example, NSAIDs.

↑↑

Strong consensus[1]

Expert consensus

[1]≥90% agreement

5.2.2 | Definite and specific triggers of CIndU

Avoidance of the specific and definite triggers of CIndUs can help to reduce the occurrence of wheals and angioedema, but usually does not suffice to control the disease and can come with a substantial burden. Patients should be provided with information that helps them to recognize and minimize relevant trigger exposure. Patients with delayed pressure urticaria, for example, should be informed that pressure is defined as force per area and that simple measures, such as broadening

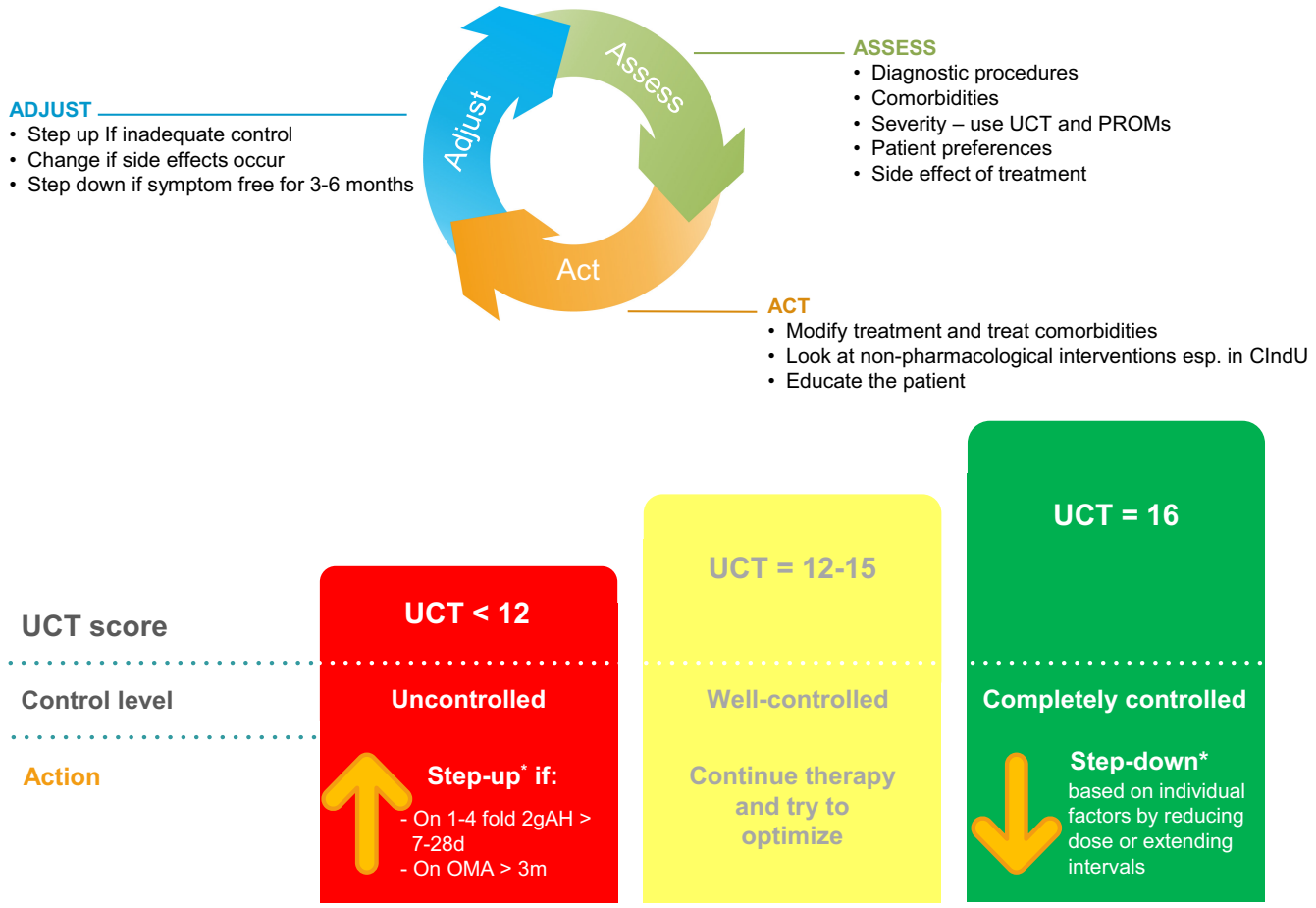


FIGURE 3 Chronic urticaria: Management decisions and treatment adjustments. CIndU: chronic inducible urticaria; d: days; m: months; PROMs: patient-reported outcome measures; OMA: omalizumab ; 2gAH: 2nd generation H_1-antihistamine; UCT: Urticaria Control Test

of the handle of heavy bags may be helpful in the prevention of symptoms. Similar considerations hold for cold urticaria where the impact of the wind chill factor in cold winds needs to be remembered. For solar urticaria, the exact identification of the range of eliciting wavelengths may be important for the appropriate selection of sunscreens or for the selection of light bulbs with an UV-A filter. However, in many patients, the threshold for the relevant physical trigger is low and total avoidance of symptoms is virtually impossible. For example, severe symptomatic dermographism is sometimes confused with CSU because seemingly spontaneous hives are observed where even loose-fitting clothing rubs on the patient's skin or unintentional scratching by patients readily causes the development of wheals in that area.

5.2.3 | Infections and inflammatory processes

In contrast to CIndU, CSU has been reported to be associated with a variety of inflammatory or infectious diseases. This is regarded as significant in some instances, but studies show conflicting results and have methodological weaknesses. Infections that may contribute to CSU disease activity include those of the gastrointestinal tract like *H. pylori* infection and bacterial infections of the nasopharynx[63] (even if association with urticaria is not clear in the individual patient and a meta-analysis shows overall low evidence for eradication therapy,[63] *H. pylori* should be eliminated as an association with gastric cancer is suggested[64]). Bowel parasites, a rare possible cause of CSU in developed industrial countries, should be eliminated if indicated.[63,65] In the past, intestinal candidiasis was regarded as a highly important underlying cause of CSU,[63] but more recent findings fail to support a significant causative role.[66] Apart from infectious diseases, chronic inflammatory processes due to diverse other diseases have been identified as potentially triggering CSU. These can be secondary to infections. This holds particularly for gastritis, reflux esophagitis, or inflammation of the bile duct or gall bladder.[67,68] Thus, it could be shown that successful eradication of helicobacter is only having an impact on CSU if also the subsequent inflammation, that

is, gastritis and esophagitis is healed.[69] However, similar to infections, it is not easily possible to discern whether any of these are relevant causes of CSU but should be treated as many of them may be also associated with development of malignancies.

5.2.4 | Stress

Although the mechanisms of stress-induced exacerbation are not well investigated, some evidence indicates that disease activity in patients with CSU can be linked to stress.[70] Further studies are needed to characterize the prevalence and relevance of CSU exacerbation by stress as well as the underlying mechanisms.

5.2.5 | Reduction of functional autoantibodies

Direct reduction of functional autoantibodies by plasmapheresis has been shown to be of temporary benefit in some, severely affected patients.[61] Due to limited experience and high costs, this therapy is suggested for autoantibody-positive CSU patients who are unresponsive to all other forms of treatment. Autoantibodies and potentially activated T cells may also be reduced by immunosuppressive medication, such as cicloporin.[71]

5.2.6 | Food

IgE-mediated food allergy is extremely rarely the underlying cause of CSU.[72,73] If identified, the specific food allergens need to be omitted as far as possible, which leads to a remission within less than 24 h. In some CSU patients, pseudoallergic reactions (non–IgE-mediated hypersensitivity reactions) to naturally occurring food ingredients and in some cases to food additives have been observed.[72-77] A pseudoallergen-free diet, containing only low levels of natural and artificial food pseudoallergens, has been tested in different countries,[78] and also, a low histamine diet may improve symptoms in some patients.[79] Those diets are controversial and as yet unproven in well-designed double-blinded placebo-controlled studies. When used they must usually be maintained for a minimum of 2–3 weeks before beneficial effects are observed. This kind of treatment requires cooperative patients, and success rates may vary considerably due to regional differences in food and dietary habits. More research is necessary on the effects of natural and artificial ingredients of food on urticaria.

5.3 | Inducing tolerance

Inducing tolerance can be useful in some subtypes of CIndU. Examples are cold urticaria, cholinergic urticaria, and solar urticaria, where a rush therapy with UV-A has been reported to be effective within 3 days.[80] However, tolerance induction is only lasting for a few days; thus, a consistent daily exposure to the stimulus just at threshold level is required. Tolerance induction and maintenance are often not accepted by patients, for example, in the case of cold urticaria where daily cold baths/showers are needed to achieve this.

5.4 | Symptomatic pharmacological treatment

5.4.1 | The targets and aims of pharmacological therapies and the need for continued treatment

Current recommended treatment options for urticaria aim to target mast cell mediators such as histamine, or activators, such as autoantibodies. Novel treatments currently under development aim to silence mast cells via inhibitory receptors or to reduce mast cell numbers. The overall goal of all of these symptomatic treatments is to help patients to be free of signs and symptoms until their urticaria shows spontaneous remission. To achieve this, pharmacological treatment should be continuous, until no longer needed. Non-sedating 2nd generation H_1-antihistamines, for example, should be used daily, to prevent the occurrence of wheals and angioedema, rather than on demand. This is supported by their safety profile (safety data are available for several years of continuous use), the results of randomized controlled trials and real-life studies,[81,82] and their mechanism of action, that is, their inverse agonist effects on the H_1 receptor, stabilizing its inactive state. Some patients with CIndU can benefit from short-term prophylactic antihistamine treatment before relevant trigger exposure.

5.4.2 | H_1-antihistamine treatment

H_1-antihistamines have been available for the treatment of urticaria since the 1950s. The older 1st generation H_1-antihistamines have pronounced anticholinergic and sedative effects, and many interactions with alcohol and other drugs, such as analgesics, hypnotics, sedatives, and mood-elevating drugs, have been described. They can also interfere with rapid eye movement (REM) sleep and impact on learning and performance. Impairment is particularly prominent during multi-tasking and performance of complex sensorimotor tasks such as driving. In a GA²LEN position paper,[83] it is strongly recommended not to use 1st generation H_1-antihistamines any longer in allergy both for adults and especially in children. This view is shared by the WHO guideline ARIA.[84] Based on strong evidence regarding potentially serious side effects of 1st generation H_1-antihistamines (lethal overdoses have been reported), we recommend against their use for the routine management of CU as first-line agents.

Modern 2nd generation H_1-antihistamines are minimally or non-sedating and free of anticholinergic effects.[85] However, two 2nd generation H_1-antihistamines, astemizole and terfenadine, are shown to have cardiotoxic effects in patients treated with inhibitors of the cytochrome P450 (CYP) 3A4 isoenzyme, such as ketoconazole or erythromycin. Astemizole and terfenadine are no longer available in most countries, and we recommend that they are not used.

Most but not all 2nd generation H_1-antihistamines have been tested specifically in urticaria, and evidence supports the use of bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine. We recommend the use of a standard-dosed modern 2nd generation H_1-antihistamines as the first-line symptomatic treatment for urticaria. However, no recommendation can be made on which to choose because, to date, well-designed clinical trials comparing the efficacy and safety of all modern 2nd generation H_1-antihistamines in urticaria are largely lacking.

Should modern 2nd generation H_1-antihistamines be used as first-line treatment of urticaria?

We **recommend** a 2nd generation H_1-antihistamine as first-line treatment for all types of urticaria.

↑↑

Strong consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1] 100% agreement

Is an increase in the dose to up to fourfold of modern 2nd generation H_1-antihistamines useful and to be preferred over other treatments in urticaria?

We **recommend** updosing of a 2nd generation H_1-antihistamine up to fourfold in patients with chronic urticaria unresponsive to a standard-dosed 2nd generation H_1-antihistamines as second-line treatment before other treatments are considered.

↑↑

Strong consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1] ≥90% agreement

Should modern 2nd generation H_1-antihistamines be taken regularly or as needed?

We **suggest** 2nd generation H_1-antihistamines to be taken regularly for the treatment of patients with chronic urticaria.

↑

Strong consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1]≥90% agreement

Should different 2nd generation H_1-antihistamines be used at the same time?

We **suggest against** using different H_1-antihistamines at the same time.

↓

Consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1] ≥70% agreement

Several studies show the benefit of the use of a higher than standard-dosed 2nd generation H_1-antihistamines in urticaria patients[86–88] corroborating earlier studies with 1st generation H_1-antihistamines that came to the same conclusion.[89,90] Studies support the use of up to fourfold standard-dosed bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, and rupatadine.[86,87,91–94]

If there is no improvement, should higher than fourfold doses of 2nd generation H_1-antihistamines be used?

We **recommend against** using higher than fourfold standard-dosed H_1-antihistamines in chronic urticaria

↓↓

Strong consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1]≥90% agreement

In summary, these studies suggest that some patients with urticaria, who show insufficient response to a standard-dosed 2nd generation H_1-antihistamine, benefit from updosing which is preferred over mixing different 2nd generation H_1-antihistamines as their pharmacologic properties are different. We, therefore, recommend to increase the dose up to fourfold, in such patients (Figure 4). Patients need to be informed that 2nd generation H_1-antihistamine updosing is off-label and higher than fourfold is not recommended as it has not been tested. However, updosing has been suggested in the guidelines for urticaria since the year 2000 and so far no serious adverse events have been reported, nor has a side effect ever been reported in the literature attributed to long-term intake and potential accumulation.

5.4.3 | Omalizumab treatment

Omalizumab is the only other licensed treatment in urticaria for patients who do not show sufficient benefit from treatment with a 2nd generation H_1-antihistamine, and therefore the next step in the algorithm. Omalizumab (anti-IgE) has been shown to be very effective and safe in the treatment of CSU.[95-100] Omalizumab has also been reported to be effective in CIndU[101–103] including cholinergic urticaria,[104] cold urticaria,[105,106] solar urticaria,[107] heat urticaria,[108] symptomatic dermographism,[109,110] and delayed pressure urticaria.[111] In CSU, omalizumab prevents wheal and angioedema development,[112] markedly improves quality of life,[113,114] is suitable for long-term treatment,[115] and effectively treats relapse after discontinuation.[115,116] The recommended initial dose in CSU is 300 mg every 4 weeks. Dosing is independent of total serum IgE.[117]

Patients with urticaria who do not show sufficient benefit from treatment with omalizumab at the licensed dose of 300 mg every 4 weeks can be treated with omalizumab at higher doses, shorter intervals, or both. Studies support the use of omalizumab treatment at doses up to 600 mg and intervals of 2 weeks, in patients with insufficient response to standard-dosed omalizumab.[118-121] Patients need to be informed that omalizumab updosing is off-label.

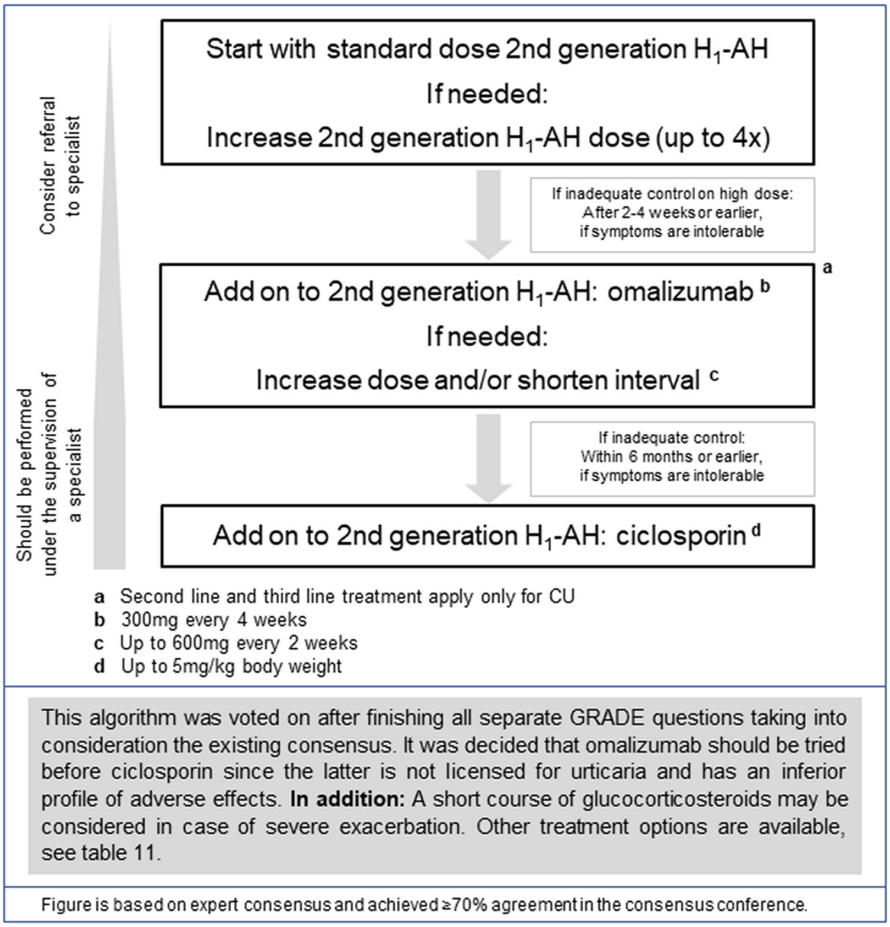


FIGURE 4 Recommended treatment algorithm for urticaria. AH: antihistamine; CU: chronic urticaria; GRADE: Grading of Recommendations Assessment, Development and Evaluation (working group). First line = High quality evidence: Low cost and worldwide availability (e.g. modern 2nd generation H1-antihistamines exist also in developing countries mostly cheaper than old sedating antihistamines), per daily dose as the half life time is much longer, very good safety profile, good efficacy. Second line (omalizumab as add on to 2nd generation H1-antihistamine) = High quality evidence: High cost, very good safety profile, very good efficacy. Third line (ciclosporin as add on) = High quality evidence: Medium to high cost, moderate safety profile, good efficacy. Short course of corticosteroids = Low quality evidence: Low cost, worldwide availability, good safety profile (for short course only), good efficacy during intake, but not suitable for long term therapy

Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H_1-antihistamines?

We **recommend** adding on omalizumab* for the treatment of patients with CU unresponsive to high dose 2nd generation H_1-antihistamines. *currently licensed for chronic spontaneous urticaria	↑↑	Strong consensus[1] Evidence- and consensus-based (see Evidence Report)

[1]≥90% agreement

Is ciclosporin useful as add-on treatment in patients unresponsive to high doses of H_1-antihistamine?

We **suggest** using ciclosporin for the treatment of patients with CU unresponsive to high dose of 2nd generation H_1-antihistamine and omalizumab.	↑	Strong consensus[1] Evidence- and consensus-based (see Evidence Report)

[1]≥90% agreement

5.4.4 | Ciclosporin treatment

Patients with urticaria who do not show sufficient benefit from treatment with omalizumab, should be treated with ciclosporin 3.5–5 mg/kg per day. Ciclosporin is immunosuppressive and has a moderate, direct effect on mast cell mediator release.[122,123] Efficacy of ciclosporin in combination with a modern 2nd generation H_1-antihistamine has been shown in placebo-controlled trials[71,124,125] as well as open controlled trials[126] in CSU, but this drug cannot be recommended as standard treatment due to a higher incidence of adverse effects.[124] Ciclosporin is off-label for urticaria and is recommended only for patients with severe disease refractory to any dose of antihistamine and omalizumab in combination. However, ciclosporin has a far better risk/benefit ratio compared with long-term use of steroids.

5.4.5 | Other symptomatic treatments

Some previous RCTs have assessed the use of leukotriene receptor antagonists. Studies are difficult to compare due to different populations studied, for example, inclusion of only aspirin and food additive intolerant patients or exclusion of ASST-positive patients. In general, the level of evidence for the efficacy of leukotriene receptor antagonists in urticaria is low but best for montelukast.

At present, topical corticosteroids are frequently and successfully used in many allergic diseases, but in urticaria topical steroids are not helpful (with the possible exception of pressure urticaria on soles as alternative therapy with low evidence). If systemic corticosteroids are used, doses between 20 and 50mg/d of prednisone equivalent are needed (dose is appropriate for adults and not children). Because such

high doses will have side effects over the long term, we strongly recommend against the use of corticosteroids outside specialist clinics. Depending on the country, it must be noted that steroids are also not licensed for CU (eg, in Germany prednisolone is only licensed for acute urticaria). For acute urticaria and acute exacerbations of CSU, a short course of oral corticosteroids, that is, treatment of a maximum of up to 10 days, may, however, be helpful to reduce disease duration/activity.[127,128] Nevertheless, well-designed RCTs are lacking.

Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?

We **recommend against** the long-term use of systemic glucocorticosteroids in CU.	↓↓	Strong consensus[1]
We **suggest** considering a short course of rescue systemic glucocorticosteroids in patients with an acute exacerbation of CU.	↑	Evidence- and consensus-based (see Evidence Report)

[1]≥90% agreement

While antihistamines at up to quadruple the manufacturers' recommended dosages will control symptoms in a large part of patients with urticaria in general practice, alternative treatments are needed for the remaining unresponsive patients. It is strongly recommended to stick to the algorithm but it is acknowledged that omalizumab has restrictions due to its high cost and ciclosporin due to its safety profile.

Since the severity of urticaria may fluctuate, and spontaneous remission may occur at any time, it is also recommended to re-evaluate the necessity for continued or alternative drug treatment every 3–6 months. This is also reflected in Figure 3.

All treatments not listed in the treatment algorithm (Figure 4) are based on clinical trials with low levels of evidence (Table 11).

H_2-antagonists and dapsone, recommended in the previous versions of the guideline, are now perceived to have little evidence to maintain them as recommendable in the algorithm but they may still have relevance as they are very affordable in some more restricted healthcare systems. Sulfasalazine, methotrexate, interferon, plasmapheresis, phototherapy, intravenous immunoglobulins (IVIG/IGIV), and other treatment options have low-quality evidence or just case series have been published[2] (Table 11). Despite the lack of published evidence, all these drugs may be of value to individual patients in the appropriate clinical context.[129]

Are H_2-antihistamines useful as add-on treatment in patients unresponsive to low or high doses of H_1-antihistamines?

We **cannot make a recommendation** for or against the combined use of H_1- and H_2-antihistamines in patients with chronic urticaria.	0	Strong consensus[1] Expert consensus

[1] ≥90% agreement

Antagonists of tumor necrosis factor alpha (TNF-alpha)[130] and IVIG,[131–134] which have been successfully used in case reports, are recommended currently only to be used in specialized centers as last option (ie, anti-TNF-alpha for delayed pressure urticaria and IVIG/IGIV for CSU).[135,136]

For the treatment of CSU and symptomatic dermographism, UV-B (narrow band-UVB, TL01), UV-A, and PUVA treatment for 1–3 months can be added to antihistamine treatment[137–139] but caution should be taking regarding the carcinogenic properties of UV light treatment.

Some treatment alternatives formerly proposed have been shown to be ineffective in double-blind, placebo-controlled studies and should no longer be used as the grade of recommendation is low. These include tranexamic acid and sodium cromoglycate in CSU,[140,141] nifedipine in symptomatic dermographism/urticaria factitia[142] and colchicine and indomethacin in delayed pressure urticaria.[143,144] However, more research may be needed for patient subgroups, for example, a pilot study[145] of patients with elevated D-dimer levels showed heparin and tranexamic acid therapy may be effective.

Could any other treatment options be recommended for the treatment of urticaria?

We **cannot make a recommendation** with respect to further treatment options as standard therapies, but these may be considered in special cases, which also include those where financial or legal limitations for the recommended algorithm treatment exist.	0	Strong consensus[1] Expert consensus

[1]≥90% agreement

5.5 | Treatment of special populations

5.5.1 | Children

Many clinicians use 1st generation H_1-antihistamines as their first choice treatment of children with urticaria assuming that their safety profile is better known than that of the modern 2nd generation H_1-antihistamines due to a longer experience with them. Also, the use of modern 2nd generation H_1-antihistamines is not licensed for use in children less than 6 months of age in many countries. However, 1st generation H_1-antihistamines have an inferior safety profile compared with 2nd generation H_1-antihistamines, and are, therefore, not recommended as first-line treatment in children with urticaria. 2nd generation H_1-antihistamines with proven efficacy and safety in the pediatric population include bilastine,[146] cetirizine,[147] desloratadine,[148,149] fexofenadine,[150] levocetirizine,[151] loratadine,[147] and rupatadine.[152] The choice of which 2nd generation H_1-antihistamines to use in children with urticaria should take into consideration the age and availability as not all are available as syrup or fast dissolving tablet suitable for children. The lowest licensed age also differs from country to country. All further steps should be based on individual considerations and be taken carefully as updosing of antihistamines, and further treatment options are not well studied in children. In addition, a short course of corticosteroids as advised in the algorithm should be used as only a very restricted measure in children.

TABLE 11 Alternative treatment options

Although evidence from publications is low, clinical experience indicates that they may be useful in certain contexts. Interventions are listed in alphabetical order by frequency of use rather than efficacy.		
Intervention	**Substance (class)**	**Indication**
Widely used		
Antidepressant	Doxepin[a]	CSU
Diet	Pseudoallergen-free diet[b]	CSU
H_2-antihistamine	Ranitidine[c]	CSU
Immunosuppressive	Methotrexate^Mycophenolate mofetil	CSU +/− DPU[d] Autoimmune CSU
Leukotriene receptor antagonist	Montelukast	CSU, DPU
Sulphones	Dapsone, Sulphasalazine	CSU +/− DPU CSU +/− DPU
Infrequently used		
Anabolic steroid	Danazol	Cholinergic urticaria
Anticoagulant	Warfarin	CSU
Antifibrinolytic	Tranexamic acid	CSU with angioedema
Immunomodulator	IVIG^Plasmapheresis	Autoimmune CSU Autoimmune CSU
Miscellaneous	Autologous blood/serum Hydroxychloroquine	CSU CSU
Phototherapy	Narrow-band UVB	Symptomatic dermographism
Psychotherapy	Holistic medicine	CSU
Rarely used		
Anticoagulant	Heparin	CSU
Immunosuppressive	Cyclophosphamide Rituximab	Autoimmune CSU Autoimmune CSU
Miscellaneous	Anakinra	DPU
	Anti-TNF-alpha	CSU +/− DPU
	Camostat mesilate	CSU
	Colchicine	CSU
	Miltefosine	CSU
	Mirtazepine	CSU
	PUVA	CSU
Very rarely used		
Immunosuppressive	Tacrolimus	CSU
Miscellaneous	Vitamin D	CSU
	Interferon alpha	CSU

[a]Has also H_1 and H_2-antihistaminergic properties.

[b]Does include low histamine diet as pseudoallergen-free diet is also low in histamine.

[c]No longer available in most countries; alternative H2-antihistamines are available including famotidine and nizatidine but evidence for their use in chronic urticaria varies.

[d]Treatment can be considered especially if CSU and DPU are co-existent in a patient.

Should the same treatment algorithm be used in children?		
We **suggest** using the same treatment algorithm with caution (eg, weight-adjusted dosage) in children with chronic urticaria	↑	Strong consensus[1] Expert consensus

[1]≥90% agreement

5.5.2 | Pregnant and lactating women

The same considerations in principle apply to pregnant and lactating women. In general, use of any systemic treatment should generally be avoided in pregnant women, especially in the first trimester. On the contrary, pregnant women have the right to the best therapy possible. While the safety of treatment has not

been systematically studied in pregnant women with urticaria, it should be pointed out that the possible negative effects of increased levels of histamine receptor binding occurring in urticaria have also not been studied in pregnancy. Regarding treatment, no reports of birth defects in women having used modern 2nd generation H_1-antihistamines during pregnancy have been reported to date. However, only small sample size studies are available for cetirizine[153] and one large meta-analysis for loratadine.[154] Furthermore, as several modern 2nd generation H_1-antihistamines are now prescription free and used widely in both allergic rhinitis and urticaria, it must be assumed that many women have used these drugs especially in the beginning of pregnancy, at least before the pregnancy was confirmed. Nevertheless, since the highest safety is mandatory in pregnancy, the suggestion for the use of modern 2nd generation H_1-antihistamines is to prefer loratadine with the possible extrapolation to desloratadine and cetirizine with a possible extrapolation to levocetirizine. All H_1-antihistamines are excreted in breast milk in low concentrations. Use of 2nd generation H_1-antihistamines is advised, as nursing infants occasionally develop sedation from the old 1st generation H_1-antihistamines transmitted in breast milk.

The increased dosage of modern 2nd generation H_1-antihistamines can only be carefully suggested in pregnancy since safety studies have not been done, and with loratadine, it must be remembered that this drug is metabolized in the liver which is not the case for its metabolite desloratadine. 1st generation H_1-antihistamines should be avoided.[83] The use of omalizumab in pregnancy has been reported to be safe, and to date, there is no indication of teratogenicity.[155–158] All further steps should be based on individual considerations, with a preference for medications that have a satisfactory risk-to-benefit ratio in pregnant women and neonates with regard to teratogenicity and embryotoxicity. For example, ciclosporin, although not teratogenic, is embryo-toxic in animal models and is associated with preterm delivery and low birth weight in human infants. Whether the benefits of ciclosporin in CU are worth, the risks in pregnant women will have to be determined on a case-by-case basis. However, all decisions should be re-evaluated according to the current recommendations published by regulatory authorities.

Should the same treatment algorithm be used in pregnant women and during lactation?		
We **suggest** using the same treatment algorithm with caution both in pregnant and lactating women after risk-benefit assessment. Drugs contraindicated or not suitable in pregnancy should not be used.	↑	Strong consensus[1] Expert consensus

[1]≥90% agreement

TABLE 12 Areas of further research in urticaria

Global epidemiology, in adults and children
The socio-economic consequences
Identification of mast cell/basophil activating factors
Identification of new histological markers
Identification of serum biomarkers of urticarial activity/mast cell activation
Clarification of the role of coagulation/coagulation factors in CSU
Development of commercially available *in vitro* tests for detecting serum autoantibodies for anti-IgE and anti-FcεRI
Evaluation of IgE-auto-antibodies
Clarification of associated psychiatric /psychosomatic diseases and their impact
Pathomechanisms in antihistamine-resistant urticaria/angioedema
Double-blind control trials comparing different modern 2nd generation H_1-antihistamines in higher doses in CSU and different subtypes of urticaria
Safety profile of available treatments, long term pharmacosurveillance
Multicenter studies on the possible effect of anticoagulants (oral and heparin derivatives) on CSU
Controlled multicenter trials on the possible effect of add-on of H_2-antihistamines, montelukast, sulfones (dapsone/sulfasalazine), methotrexate, azathioprine
Development of better treatment options
Trials and licensing of 2nd generation H_1-antihistamines for the treatment of children below 6 months of age

6 | NEED FOR FURTHER RESEARCH

The panel and participants identified several areas in which further research is needed. These points are summarized in Table 12.

ACKNOWLEDGEMENTS

The authors would like to thank the physicians and specialists who contributed to the development of this update of the guidelines through their active participation in the democratic process and discussion during the 6th International Consensus Meeting on Urticaria 2020. They would also like to thank the national societies for funding their delegates.

GA2LEN-UCARE-Network (www.ga2len-ucare.com).

Endorsing societies: AAD, American Academy of Dermatology; AAIITO, Italian Association of Hospital and Territorial Allergists and Immunologists; ACAAI, American College of Allergy, Asthma and Immunology; AEDV, Spanish Academy of Dermatology and Venereology; APAAACI, Asia Pacific Association of Allergy, Asthma and Clinical Immunology; ASBAI, Brazilian Association of Allergy and Immunology; BAD, British Association of Dermatologists; BSACI, British Society for Allergy and Clinical Immunology; CDA, Chinese Dermatologist Association; CMICA, Mexican College of Clinical Immunology and Allergy; CSACI, Canadian Society of Allergy and Clinical Immunology; DAAU, Deutsche Akademie für Allergologie und Umweltmedizin; DDG, German Society of Dermatology; DDS, Danish

Dermatological Society; DGAKI, German Society of Allergology and Clinical Immunology; DSA, Danish Society for Allergology; DST, Dermatological Society of Thailand; EAACI, European Academy of Allergology and Clinical Immunology; EDF, European Dermatology Forum; EEAKA, Hellenic Society of Allergology and Clinical Immunology; EMBRN, European Mast Cell and Basophil Research Network; FDS, Finnish Dermatological Society; GA²LEN, Global Allergy and Asthma European Network; IAACI, Israel Association of Allergy and Clinical Immunology; IADVL, Indian Association of Dermatologists, Venereologists and Leprologists; JDA, Japanese Dermatological Association; JSA, Japanese Society of Allergology; MADV, Maltese Association of Dermatology & Venereology; MDT, Hungarian Dermatological Society; MSAI, Malaysian Society of Allergy and Immunology; NVvA, Dutch Society of Allergology; ÖGDV, Austrian Society of Dermatology and Venereology; PASAAI, Pan Arab Society of Allergy, Asthma and Immunology; PTA, Polish Society of Allergology; RAACI, Russian Association of Allergology and Clinical Immunology; RBSDV, Royal Belgian Society of Dermatology and Venereology; SBD, Brazilian Society of Dermatology; SBP, Brazilian Society of Paediatrics; SFD, French Society of Dermatology (Groupe Urticaire de la Société francaise de dermatologie); SGAI, Swiss Society for Allergology and Immunology; SGDV, Swiss Society of Dermatology and Venereology; SIDeMaST, Italian Society of Medical, Surgical and Aesthetic Dermatology and Sexual Transmitted Diseases; SPAAI, Paraguayan Society of Immunology, Asthma and Allergy; SPDV, Portuguese Society of Dermatology and Venereology; TDD, Turkish Society of Dermatology; TNSACI, Turkish National Society of Allergy and Clinical Immunology; UNBB, Urticaria Network Berlin-Brandenburg; UNEV, Urticaria Network; WAO, World Allergy Organization.

CONFLICT OF INTEREST

An overview of the declarations of personal financial conflicts of interests of all authors/members of the expert panel is given in the Methods Report, which is available on the EDF website: https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html

IMPORTANT

As this is an international guideline, no comment is given regarding the licensing of the drugs mentioned for the treatment of urticaria. It is in the duty of the treating physician to adhere to the relevant local regulations.

NOTES ON USE/DISCLAIMER

This is an updated version of the international urticaria guideline. It is based on the update and revision of this guideline published in 2018: Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocatürk E, Kulthanan K, Larenas-Linnemann D, Leslie TA, Magerl M, Mathelier-Fusade P, Meshkova RY, Metz M, Nast A, Nettis E, Oude-Elberink H, Rosumeck S, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Staubach P, Sussman G, Toubi E, Vena GA, Vestergaard C, Wedi B, Werner RN, Zhao Z, Maurer M; The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-1414.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for Urticaria was developed in accordance with the EuroGuiDerm Methods Manual v1.3, which can be found on the website of the European Dermatology Forum (EDF), subsection EuroGuiDerm/EDF Guidelines at https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html.

Please see the Methods Report and separate Evidence Report for the International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria, which are available alongside the guideline document on the EDF website: https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html

ORCID

Torsten Zuberbier https://orcid.org/0000-0002-1466-8875
Amir Hamzah Abdul Latiff https://orcid.org/0000-0002-6304-0494
Riccardo Asero https://orcid.org/0000-0002-8277-1700
Christine Bangert https://orcid.org/0000-0003-3392-6590
Jonathan A. Bernstein https://orcid.org/0000-0002-3476-1196
Carsten Bindslev-Jensen https://orcid.org/0000-0002-8940-038X
Knut Brockow https://orcid.org/0000-0002-2775-3681
Zenon Brzoza https://orcid.org/0000-0002-1230-7013
Paulo R. Criado https://orcid.org/0000-0001-9785-6099
Corinna Dressler https://orcid.org/0000-0001-7075-2062
Matthew Gaskins https://orcid.org/0000-0001-6436-2703
Aslı Gelincik https://orcid.org/0000-0002-3524-9952
Margarida Gonçalo https://orcid.org/0000-0001-6842-1360
Eckard Hamelmann https://orcid.org/0000-0002-2996-8248
Michihiro Hide https://orcid.org/0000-0002-1569-6034
Allen Kaplan https://orcid.org/0000-0002-6566-4743
Désirée Larenas-Linnemann https://orcid.org/0000-0002-5713-5331
Martin Metz https://orcid.org/0000-0002-4070-9976
Charlotte G. Mortz https://orcid.org/0000-0001-8710-0829
Alexander Nast https://orcid.org/0000-0003-3504-2203
Ruby Pawankar https://orcid.org/0000-0002-3091-7237
Paolo D. Pigatto https://orcid.org/0000-0001-6599-9538
Hector Ratti Sisa https://orcid.org/0000-0001-7852-3854
Peter Schmid-Grendelmeier https://orcid.org/0000-0003-3215-3370
Bulent E. Sekerel https://orcid.org/0000-0001-7402-6850
Frank Siebenhaar https://orcid.org/0000-0003-4532-1644
Angele Soria https://orcid.org/0000-0002-8726-6658

Luca Stingeni https://orcid.org/0000-0001-7919-8141
Gordon Sussman https://orcid.org/0000-0002-2202-2513
Zahava Vadasz https://orcid.org/0000-0003-2899-5508
Bettina Wedi https://orcid.org/0000-0002-9868-6308
Zuotao Zhao https://orcid.org/0000-0002-9595-6050
Marcus Maurer https://orcid.org/0000-0002-4121-481X

REFERENCES

1. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*. 2009;64(10):1417-1426. doi:10.1111/j.1398-9995.2009.02179.x
2. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2) LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009;64(10):1427-1443. doi:10.1111/j.1398-9995.2009.02178.x
3. 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(7):868-887. doi:10.1111/all.12313
4. Zuberbier T, Aberer W, Asero R, et al. Methods report on the development of the 2013 revision and update of the EAACI/GA2 LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2014;69(7). doi:10.1111/all.12370
5. AGREE Next Steps Consortium. The AGREE II Instrument. http://www.agreetrust.org. Accessed January 12, 2015.
6. Higgins JPT, Green S, Cochrane C. Cochrane handbook for systematic reviews of interventions. Cochrane Collaboration. http://training.cochrane.org/handbook. Accessed: 27 September 2021.
7. Dressler C, Rosumeck S, Werner RN, et al. Executive summary of the methods report for 'The EAACI/GA(2) LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update'. *Allergy*. 2018;73(5):1145-1146. doi:10.1111/all.13414
8. Nordic Cochrane Centre. *Review Manager (RevMan) [Computer program]. Version 5.3*. The Cochrane Collaboration; 2014.
9. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490. doi:10.1136/bmj.328.7454.1490
10. *GRADEpro GDT: GRADEpro Guideline Development Tool*. McMaster University (developed by Evidence Prime, Inc.); 2015.
11. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ*. 1995;311(7001):376-380.
12. Kaplan AP, Garofalo J. Identification of a new physically induced urticaria: cold-induced cholinergic urticaria. *J Allergy Clin Immunol*. 1981;68(6):438-441. doi:10.1016/s0091-6749(81)90209-8
13. Church MK, Kolkhir P, Metz M, Maurer M. The role and relevance of mast cells in urticaria. *Immunol Rev*. 2018;282(1):232-247. doi:10.1111/imr.12632
14. Haas N, Schadendorf D, Henz BM. Differential endothelial adhesion molecule expression in early and late whealing reactions. *Int Arch Allergy Immunol*. 1998;115(3):210-214.
15. Peteiro C, Toribio J. Incidence of leukocytoclastic vasculitis in chronic idiopathic urticaria. Study of 100 cases. *Am J Dermatopathol*. 1989;11(6):528-533.
16. Ito Y, Satoh T, Takayama K, Miyagishi C, Walls AF, Yokozeki H. Basophil recruitment and activation in inflammatory skin diseases. *Allergy*. 2011;66(8):1107-1113. doi:10.1111/j.1398-9995.2011.02570.x
17. Kay AB, Clark P, Maurer M, Ying S. Elevations in T-helper-2-initiating cytokines (interleukin-33, interleukin-25 and thymic stromal lymphopoietin) in lesional skin from chronic spontaneous ('idiopathic') urticaria. *Br J Dermatol*. 2015;172(5):1294-1302. doi:10.1111/bjd.13621
18. Kay AB, Ying S, Ardelean E, et al. Calcitonin gene-related peptide and vascular endothelial growth factor are expressed in lesional but not uninvolved skin in chronic spontaneous urticaria. *Clin Exp Allergy*. 2014;44(8):1053-1060. doi:10.1111/cea.12348
19. Kay AB, Ying S, Ardelean E, et al. Elevations in vascular markers and eosinophils in chronic spontaneous urticarial weals with low-level persistence in uninvolved skin. *Br J Dermatol*. 2014;171(3):505-511. doi:10.1111/bjd.12991
20. Greaves MW. Chronic urticaria. *N Engl J Med*. 1995;332(26):1767-1772. doi:10.1056/NEJM199506293322608
21. Kaplan AP. Clinical practice. Chronic urticaria and angioedema. *N Engl J Med*. 2002;346(3):175-179. doi:10.1056/NEJMcp011186
22. Hermes B, Prochazka AK, Haas N, Jurgovsky K, Sticherling M, Henz BM. Upregulation of TNF-alpha and IL-3 expression in lesional and uninvolved skin in different types of urticaria. *J Allergy Clin Immunol*. 1999;103(2 Pt 1):307-314.
23. Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy*. 2011;66(3):317-330. doi:10.1111/j.1398-9995.2010.02496.x
24. Gonçalo M, Gimenéz-Arnau A, Al-Ahmad M, et al. The global burden of chronic urticaria for the patient and society. *Br J Dermatol*. 2021;184(2):226-236. doi:10.1111/bjd.19561
25. Baiardini I, Braido F, Bindslev-Jensen C, et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in patients with urticaria: a GA(2) LEN taskforce position paper. *Allergy*. 2011;66(7):840-844. doi:10.1111/j.1398-9995.2011.02580.x
26. Maurer M, Staubach P, Raap U, et al. H1-antihistamine-refractory chronic spontaneous urticaria: it's worse than we thought - first results of the multicenter real-life AWARE study. *Clin Exp Allergy*. 2017;47(5):684-692. doi:10.1111/cea.12900
27. Maurer M, Staubach P, Raap U, Richter-Huhn G, Baier-Ebert M, Chapman-Rothe N. ATTENTUS, a German online survey of patients with chronic urticaria highlighting the burden of disease, unmet needs and real-life clinical practice. *Br J Dermatol*. 2016;174(4):892-894. doi:10.1111/bjd.14203
28. Maurer M, Abuzakouk M, Bérard F, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy*. 2017;72(12):2005-2016. doi:10.1111/all.13209
29. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol*. 1997;136(2):197-201.
30. Baiardini I, Giardini A, Pasquali M, et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy*. 2003;58(7):621-623.
31. Parisi CA, Ritchie C, Petriz N, Morelo TC. Direct Medical Costs of Chronic Urticaria in a Private Health Organization of Buenos Aires, Argentina. *Value Health Reg Issues*. 2016;11:57-59. doi:10.1016/j.vhri.2016.07.008
32. Broder MS, Raimundo K, Antonova E, Chang E. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. *Am J Clin Dermatol*. 2015;16(4):313-321. doi:10.1007/s40257-015-0134-8
33. Graham J, McBride D, Stull D, et al. Cost utility of omalizumab compared with standard of care for the treatment of chronic spontaneous urticaria. *Pharmacoeconomics*. 2016;34(8):815-827. doi:10.1007/s40273-016-0412-1
34. Metz M, Altrichter S, Buttgereit T, et al. Diagnostic workup in chronic spontaneous urticaria – what to test and why? *J Allergy Clin Immunol Pract*. 2021;9:2274-2283.
35. 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. *Allergy*. 2018;73(7):1393-1414. doi:10.1111/all.13397

36. Curto-Barredo L, Archilla LR, Vives GR, Pujol RM, Giménez-Arnau AM. Clinical features of chronic spontaneous urticaria that predict disease prognosis and refractoriness to standard treatment. *Acta Derm Venereol*. 2018;98(7):641-647. doi:10.2340/00015555-2941
37. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. *Allergy*. 2021;76:2965-2981. doi:10.1111/all.14757
38. Maurer M, Eyerich K, Eyerich S, et al. Urticaria: collegium internationale allergologicum (CIA) update 2020. *Int Arch Allergy Immunol*. 2020;181(5):321-333. doi:10.1159/000507218
39. Weller K, Zuberbier T, Maurer M. Clinically relevant outcome measures for assessing disease activity, disease control and quality of life impairment in patients with chronic spontaneous urticaria and recurrent angioedema. *Curr Opin Allergy Clin Immunol*. 2015;15(3):220-226. doi:10.1097/aci.0000000000000163
40. Mlynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy*. 2008;63(6):777-780.
41. Hawro T, Ohanyan T, Schoepke N, et al. Comparison and interpretability of the available urticaria activity scores. *Allergy*. 2017;73(1):251-255. doi:10.1111/all.13271
42. Weller KG, Magerl M, Tohme M, et al. Development, validation and initial results of the angioedema activity score. *Allergy*. 2013;68(9):1185-1192.
43. Ohanyan T, Schoepke N, Bolukbasi B, et al. Responsiveness and minimal important difference of the urticaria control test. *J Allergy Clin Immunol*. 2017;140(6):1710-1713. doi:10.1016/j.jaci.2017.04.050
44. Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol*. 2014;133(5):1365-1372. doi:10.1016/j.jaci.2013.12.1076
45. Magerl M, Altrichter S, Borzova E, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. *Allergy*. 2016;71(6):780-802. doi:10.1111/all.12884
46. Magerl M, Abajian M, Krause K, Altrichter S, Siebenhaar F, Church MK. An improved Peltier effect-based instrument for critical temperature threshold measurement in cold- and heat-induced urticaria. *J Eur Acad Dermatol Venereol*. 2015;29(10):2043-2045. doi:10.1111/jdv.12739
47. Schoepke N, Abajian M, Church MK, Magerl M. Validation of a simplified provocation instrument for diagnosis and threshold testing of symptomatic dermographism. *Clin Exp Dermatol*. 2015;40(4):399-403. doi:10.1111/ced.12547
48. Mlynek A, Vieira dos Santos R, Ardelean E, et al. A novel, simple, validated and reproducible instrument for assessing provocation threshold levels in patients with symptomatic dermographism. *Clin Exp Dermatol*. 2013;38(4):360-366; quiz 366. doi:10.1111/ced.12107
49. Altrichter S, Salow J, Ardelean E, Church MK, Werner A, Maurer M. Development of a standardized pulse-controlled ergometry test for diagnosing and investigating cholinergic urticaria. *J Dermatol Sci*. 2014;75(2):88-93. doi:10.1016/j.jdermsci.2014.04.007
50. Koch K, Weller K, Werner A, Maurer M, Altrichter S. Antihistamine updosing reduces disease activity in patients with difficult-to-treat cholinergic urticaria. *J Allergy Clin Immunol*. 2016;138(5):1483-1485. doi:10.1016/j.jaci.2016.05.026
51. Ruft J, Asady A, Staubach P, et al. Development and validation of the Cholinergic Urticaria Quality-of-Life Questionnaire (CholU-QoL). *Clin Exp Allergy*. 2018;48(4):433-444. doi:10.1111/cea.13102
52. Azkur D, Civelek E, Toyran M, et al. Clinical and etiologic evaluation of the children with chronic urticaria. *Allergy Asthma Proc*. 2016;37(6):450-457.
53. Lee SJ, Ha EK, Jee HM, et al. Prevalence and risk factors of urticaria with a focus on chronic urticaria in children. *Allergy Asthma Immunol Res*. 2017;9(3):212-219. doi:10.4168/aair.2017.9.3.212
54. Church MK, Weller K, Stock P, Maurer M. Chronic spontaneous urticaria in children: itching for insight. *Pediatr Allergy Immunol*. 2011;22(1 Pt 1):1-8. doi:10.1111/j.1399-3038.2010.01120.x
55. Maurer M, Church MK, Weller K. Chronic urticaria in children - still itching for insight. *JAMA Dermatol*. 2017;153(12):1221-1222.
56. Fricke J, Ávila G, Keller T, et al. Prevalence of chronic urticaria in children and adults across the globe: systematic review with meta-analysis. *Allergy*. 2020;75(2):423-432. doi:10.1111/all.14037
57. Balp MM, Weller K, Carboni V, et al. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. *Pediatr Allergy Immunol*. 2018;29(6):630-636. doi:10.1111/pai.12910
58. Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol*. 2004;21(2):102-108. doi:10.1111/j.0736-8046.2004.21202.x
59. Staubach P, Mann C, Peveling-Oberhag A, et al. Epidemiology of urticaria in German children. *J Dtsch Dermatol Ges*. 2021;19(7):1013-1019. doi:10.1111/ddg.14485
60. Kuemmerle-Deschner JB, Ozen S, Tyrrell PN, et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). *Ann Rheum Dis*. 2017;76(6):942-947. doi:10.1136/annrheumdis-2016-209686
61. Grattan CE, Francis DM, Slater NG, Barlow RJ, Greaves MW. Plasmapheresis for severe, unremitting, chronic urticaria. *Lancet*. 1992;339(8801):1078-1080. doi:10.1016/0140-6736(92)90666-Q
62. Kowalski ML, Woessner K, Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema. *J Allergy Clin Immunol*. 2015;136(2):245-251. doi:10.1016/j.jaci.2015.06.021
63. Shakouri A, Compalati E, Lang DM, Khan DA. Effectiveness of Helicobacter pylori eradication in chronic urticaria: evidence-based analysis using the Grading of Recommendations Assessment, Development, and Evaluation system. *Curr Opin Allergy Clin Immunol*. 2010;10(4):362-369. doi:10.1097/ACI.0b013e32833c79d7
64. Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: a state of the art review. *Gastroenerol Hepatol Bed Bench*. 2015;8(Suppl1):6-14.
65. Henz BM, Zuberbier T. Causes of urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. *Urticaria*. Springer; 1998.
66. Ergon MC, iĺknur T, Yućesoy M, Oźkan Ş. Candida spp. colonization and serum anticandidal antibody levels in patients with chronic urticaria. *Clin Exp Dermatol*. 2007;32(6):740-743. doi:10.1111/j.1365-2230.2007.02512.x
67. Zuberbier T, ChantraineKess S, Hartmann K, Czarnetzki BM. Pseudoallergen-free diet in the treatment of chronic urticaria - A prospective study. *Acta Derm Venereol*. 1995;75(6):484-487.
68. Bruno G, Andreozzi P. U. G. Exercise-induced urticaria-angioedema syndrome: A role in gastroesophageal reflux. In: Vena GAPP, editor. *Proceedings of the international symposium on urticaria*. Editrice CSH, Milan. 1998:85-89.
69. Zheleznov S, Urzhumtseva G, Petrova N, et al. Gastritis can cause and trigger chronic spontaneous urticaria independent of the presence of *Helicobacter pylori*. *Int Arch Allergy Immunol*. 2018;175(4):246-251. doi:10.1159/000487669
70. Varghese R, Rajappa M, Chandrashekar L, et al. Association among stress, hypocortisolism, systemic inflammation, and disease severity in chronic urticaria. *Ann Allergy Asthma Immunol*. 2016;116(4):344-348. doi:10.1016/j.anai.2016.01.016
71. Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol*. 2000;143(2):365-372.

72. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. *Acta Derm Venereol*. 1995;75(6):484-487.
73. Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol*. 1981;104(4):369-381.
74. Pfrommer CBR, Vieths S, Ehlers I, Henz BM, Zuberbier T. Characterization of naturally occurring pseudoallergens causing chronic urticaria. *J Allergy Clin Immunol*. 1996;97(367).
75. Pigatto PD, Valsecchi RH. Chronic urticaria: a mystery. *Allergy*. 2000;55(3):306-308.
76. Bunselmeyer B, Laubach HJ, Schiller M, Stanke M, Luger TA, Brehler R. Incremental build-up food challenge–a new diagnostic approach to evaluate pseudoallergic reactions in chronic urticaria: a pilot study: stepwise food challenge in chronic urticaria. *Clin Exp Allergy*. 2009;39(1):116-126.
77. Nettis E, Colanardi MC, Ferrannini A, Tursi A. Sodium benzoate-induced repeated episodes of acute urticaria/angio-oedema: randomized controlled trial. *Br J Dermatol*. 2004;151(4):898-902. doi:10.1111/j.1365-2133.2004.06095.x
78. Akoglu G, Atakan N, Cakir B, Kalayci O, Hayran M. Effects of low pseudoallergen diet on urticarial activity and leukotriene levels in chronic urticaria. *Arch Dermatol Res*. 2012;304(4):257-262. doi:10.1007/s00403-011-1203-3
79. Wagner N, Dirk D, Peveling-Oberhag A, et al. A Popular myth - low-histamine diet improves chronic spontaneous urticaria - fact or fiction? *J Eur Acad Dermatol Venereol*. 2016;31(4):650-655.
80. Beissert S, Stander H, Schwarz T. UVA rush hardening for the treatment of solar urticaria. *J Am Acad Dermatol*. 2000;42(6):1030-1032.
81. Grob JJ, Auquier P, Dreyfus I, Ortonne JP. How to prescribe antihistamines for chronic idiopathic urticaria: desloratadine daily vs PRN and quality of life. *Allergy*. 2009;64(4):605-612. doi:10.1111/j.1398-9995.2008.01913.x
82. Weller K, Ardelean E, Scholz E, Martus P, Zuberbier T, Maurer M. Can on-demand non-sedating antihistamines improve urticaria symptoms? A double-blind, randomized, single-dose study. *Acta Derm Venereol*. 2013;93(2):168-174. doi:10.2340/00015555-1434
83. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy*. 2010;65(4):459-466. doi:10.1111/j.1398-9995.2009.02325.x
84. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8-160. doi:10.1111/j.1398-9995.2007.01620.x
85. Kubo N, Senda M, Ohsumi Y, et al. Brain histamine H1 receptor occupancy of loratadine measured by positron emission topography: comparison of H1 receptor occupancy and proportional impairment ratio. *Hum Psychopharmacol*. 2011;26(2):133-139. doi:10.1002/hup.1184
86. Kontou-Fili K, Paleologos G, Herakleous M. Suppression of histamine-induced skin reactions by loratadine and cetirizine diHCl. *Eur J Clin Pharmacol*. 1989;36(6):617-619.
87. Zuberbier T, Munzberger C, Haustein U, et al. Double-blind crossover study of high-dose cetirizine in cholinergic urticaria. *Dermatology*. 1996;193(4):324-327.
88. Kontou-Fili KM, Demaka P, Paleologos G. Therapeutic effect of cetirizine 2 HCl in delayed pressure urticaria. *Health Sci Rev*. 1989;3:23-25.
89. Wanderer AA, Ellis EF. Treatment of cold urticaria with cyproheptadine. *J Allergy Clin Immunol*. 1971;48(6):366-371. doi:10.1016/0091-6749(71)90083-2
90. Kaplan AP, Gray L, Shaff RE, Horakova Z, Beaven MA. In vivo studies of mediator release in cold urticaria and cholinergic urticaria. *J Allergy Clin Immunol*. 1975;55(6):394-402. doi:10.1016/0091-6749(75)90078-0
91. Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125(3):676-682. doi:10.1016/j.jaci.2009.11.047
92. Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. *J Allergy Clin Immunol*. 2009;123(3):672-679.
93. Gimenez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo- controlled treatment with rupatadine 10 and 20 mg. *J Eur Acad Dermatol Venereol*. 2009;23(9):1088-1091. doi:10.1111/j.1468-3083.2009.03289.x
94. Guillen-Aguinaga S, Jauregui Presa I, Aguinaga-Ontoso E, Guillen-Grima F, Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. *Br J Dermatol*. 2016;175(6):1153-1165. doi:10.1111/bjd.14768
95. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H-1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128(3):567-573. doi:10.1016/j.jaci.2011.06.010
96. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128(1):202-209. doi:10.1016/j.jaci.2011.04.038
97. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2015;135(1):67-75. doi:10.1038/jid.2014.306
98. Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368(10):924-935. doi:10.1056/NEJMoa1215372
99. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132(1):101-109. doi:10.1016/j.jaci.2013.05.013
100. Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137(6):1742-1750. doi:10.1016/j.jaci.2015.12.1342
101. Maurer M, Metz M, Brehler R, et al. Omalizumab treatment in chronic inducible urticaria: a systematic review of published evidence. *J Allergy Clin Immunol*. 2017;141:638-649. doi:10.1016/j.jaci.2017.06.032
102. Metz M, Altrichter S, Ardelean E, et al. Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. *Int Arch Allergy Immunol*. 2011;154(2):177-180. doi:10.1159/000320233
103. Exposito-Serrano V, Curto-Barredo L, Aguilera Peiro P, et al. Omalizumab for the treatment of chronic inducible urticaria in 80 patients. *Br J Dermatol*. 2021;184(1):167-168. doi:10.1111/bjd.19425
104. Metz M, Bergmann P, Zuberbier T, Maurer M. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. *Allergy*. 2008;63(2):247-249.
105. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol*. 2006;117(6):1415-1418. doi:10.1016/j.jaci.2006.04.003
106. Metz M, Schutz A, Weller K, et al. Omalizumab is effective in cold urticaria-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol*. 2017;140(3):864-867. doi:10.1016/j.jaci.2017.01.043
107. Guzelbey O, Ardelean E, Magerl M, Zuberbier T, Maurer M, Metz M. Successful treatment of solar urticaria with anti-immunoglobulin E therapy. *Allergy*. 2008;63(11):1563-1565.

108. Bullerkotte U, Wieczorek D, Kapp A, Wedi B. Effective treatment of refractory severe heat urticaria with omalizumab. *Allergy*. 2010;65(7):931-932. doi:10.1111/j.1398-9995.2009.02268.x
109. Krause K, Ardelean E, Kessler B, et al. Antihistamine-resistant urticaria factitia successfully treated with anti-immunoglobulin E therapy. *Allergy*. 2010;65(11):1494-1495. doi:10.1111/j.1398-9995.2010.02409.x
110. Maurer M, Schütz A, Weller K, et al. Omalizumab is effective in symptomatic dermographism-results of a randomized placebo-controlled trial. *J Allergy Clin Immunol*. 2017;140(3):870-873. doi:10.1016/j.jaci.2017.01.042
111. Bindslev-Jensen C, Skov PS. Efficacy of omalizumab in delayed pressure urticaria: a case report. *Allergy*. 2010;65(1):138-139. doi:10.1111/j.1398-9995.2009.02188.x
112. Staubach P, Metz M, Chapman-Rothe N, et al. Effect of omalizumab on angioedema in H1 -antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial. *Allergy*. 2016;71(8):1135-1144. doi:10.1111/all.12870
113. Finlay AY, Kaplan AP, Beck LA, et al. Omalizumab substantially improves dermatology-related quality of life in patients with chronic spontaneous urticaria. *J Eur Acad Dermatol Venereol*. 2017;31(10):1715-1721. doi:10.1111/jdv.14384
114. Maurer M, Sofen H, Ortiz B, Kianifard F, Gabriel S, Bernstein JA. Positive impact of omalizumab on angioedema and quality of life in patients with refractory chronic idiopathic/spontaneous urticaria: analyses according to the presence or absence of angioedema. *J Eur Acad Dermatol Venereol*. 2017;31(6):1056-1063. doi:10.1111/jdv.14075
115. Maurer M, Kaplan A, Rosén K, et al. The XTEND-CIU study: long term use of Omalizumab in Chronic Idiopathic Urticaria. *J Allergy Clin Immunol*. 2017;141(3):1138-1139.
116. Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. *JAMA Dermatol*. 2014;150(3):288-290. doi:10.1001/jamadermatol.2013.8705
117. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H-1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128(3):567. doi:10.1016/j.jaci.2011.06.010
118. Summary of Product Characteristics – Xolair (omalizumab). Novartis Europharm Limited. [Date of issue of marketing authorisation 25 Oct 2005].
119. Metz M, Vadasz Z, Kocatürk E, Giménez-Arnau AM. Omalizumab updosing in chronic spontaneous urticaria: an overview of real-world evidence. *Clin Rev Allergy Immunol*. 2020;59(1):38-45. doi:10.1007/s12016-020-08794-6
120. Curto-Barredo L, Spertino J, Figueras-Nart I, et al. Omalizumab updosing allows disease activity control in patients with refractory chronic spontaneous urticaria. *Br J Dermatol*. 2018;179(1):210-212. doi:10.1111/bjd.16379
121. Kocatürk E, Deza G, Kızıltaç K, Giménez-Arnau AM. Omalizumab updosing for better disease control in chronic spontaneous urticaria patients. *Int Arch Allergy Immunol*. 2018;177(4):360-364. doi:10.1159/000491530
122. Stellato C, de Paulis A, Ciccarelli A, et al. Anti-inflammatory effect of cyclosporin A on human skin mast cells. *J Invest Dermatol*. 1992;98(5):800-804.
123. Harrison CA, Bastan R, Peirce MJ, Munday MR, Peachell PT. Role of calcineurin in the regulation of human lung mast cell and basophil function by cyclosporine and FK506. *Br J Pharmacol*. 2007;150(4):509-518. doi:10.1038/sj.bjp.0707002
124. Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol*. 2006;55(4):705-709. doi:10.1016/j.jaad.2006.04.078
125. Kulthanan K, Chaweekulrat P, Komoltri C, et al. Cyclosporine for chronic spontaneous urticaria: a meta-analysis and systematic review. *J Allergy Clin Immunol Pract*. 2018;6:586-599.
126. Doshi DR, Weinberger MM. Experience with cyclosporine in children with chronic idiopathic urticaria. *Pediatr Dermatol*. 2009;26(4):409-413. doi:10.1111/j.1525-1470.2009.00869.x
127. Zuberbier T, Ifflander J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm Venereol*. 1996;76(4):295-297.
128. Asero R, Tedeschi A. Usefulness of a short course of oral prednisone in antihistamine-resistant chronic urticaria: a retrospective analysis. *J Invest Allerg Clin*. 2010;20(5):386-390.
129. Rutkowski K, Grattan CEH. How to manage chronic urticaria 'beyond' guidelines: a practical algorithm. *Clin Exp Allergy*. 2017;47(6):710-718.
130. Magerl M, Philipp S, Manasterski M, Friedrich M, Maurer M. Successful treatment of delayed pressure urticaria with anti-TNF-alpha. *J Allergy Clin Immun*. 2007;119(3):752-754. doi:10.1016/j.jaci.2006.12.658
131. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol*. 1998;138(1):101-106.
132. Dawn G, Urcelay M, Ah-Weng A, O'Neill SM, Douglas WS. Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. *Br J Dermatol*. 2003;149(4):836-840.
133. Pereira C, Tavares B, Carrapatoso I, et al. Low-dose intravenous gammaglobulin in the treatment of severe autoimmune urticaria. *Eur Ann Allergy Clin Immunol*. 2007;39(7):237-242.
134. Mitzel-Kaoukhov H, Staubach P, Muller-Brenne T. Effect of high-dose intravenous immunoglobulin treatment in therapy-resistant chronic spontaneous urticaria. *Ann Allergy Asthma Immunol*. 2010;104(3):253-258. doi:10.1016/j.anai.2009.12.007
135. Bangsgaard N, Skov L, Zachariae C. Treatment of refractory chronic spontaneous urticaria with adalimumab. *Acta Derm Venereol*. 2017;97(4):524-525. doi:10.2340/00015555-2573
136. Sand FL, Thomsen SF. TNF-alpha inhibitors for chronic urticaria: experience in 20 patients. *J Allergy (Cairo)*. 2013;2013:1–4. doi:10.1155/2013/130905
137. Hannuksela M, Kokkonen EL. Ultraviolet light therapy in chronic urticaria. *Acta Derm Venereol*. 1985;65(5):449-450.
138. Borzova E, Rutherford A, Konstantinou GN, Leslie KS, Grattan CEH. Narrowband ultraviolet B phototherapy is beneficial in antihistamine-resistant symptomatic dermographism: a pilot study. *J Am Acad Dermatol*. 2008;59(5):752-757. doi:10.1016/j.jaad.2008.07.016
139. Engin B, Ozdemir M, Balevi A, Mevlitoglu I. Treatment of chronic urticaria with narrowband ultraviolet B phototherapy: a randomized controlled trial. *Acta Derm Venereol*. 2008;88(3):247-251. doi:10.2340/00015555-0434
140. Thormann J, Laurberg G, Zachariae H. Oral sodium cromoglycate in chronic urticaria. *Allergy*. 1980;35(2):139-141.
141. Laurberg G. Tranexamic acid (Cyklokapron) in chronic urticaria: a double-blind study. *Acta Derm Venereol*. 1977;57(4):369-370.
142. Lawlor F, Ormerod AD, Greaves MW. Calcium antagonist in the treatment of symptomatic dermographism. Low-dose and high-dose studies with nifedipine. *Dermatologica*. 1988;177(5):287-291.
143. Lawlor F, Black AK, Ward AM, Morris R, Greaves MW. Delayed pressure urticaria, objective evaluation of a variable disease using a dermographometer and assessment of treatment using colchicine. *Br J Dermatol*. 1989;120(3):403-408.
144. Dover JS, Black AK, Ward AM, Greaves MW. Delayed pressure urticaria. Clinical features, laboratory investigations, and response to therapy of 44 patients. *J Am Acad Dermatol*. 1988;18(6):1289-1298.
145. Asero R, Tedeschi A, Cugno M. Heparin and tranexamic Acid therapy may be effective in treatment-resistant chronic urticaria

with elevated d-dimer: a pilot study. *Int Arch Allergy Immunol*. 2010;152(4):384-389. doi:10.1159/000292947

146. Novak Z, Yanez A, Kiss I, et al. Safety and tolerability of bilastine 10 mg administered for 12 weeks in children with allergic diseases. *Pediatr Allergy Immunol*. 2016;27(5):493-498. doi:10.1111/pai.12555
147. Nayak AS, Berger WE, LaForce CF, et al. Randomized, placebo-controlled study of cetirizine and loratadine in children with seasonal allergic rhinitis. *Allergy Asthma Proc*. 2017;38(3):222-230. doi:10.2500/aap.2017.38.4050
148. Gupta S, Khalilieh S, Kantesaria B, Banfield C. Pharmacokinetics of desloratadine in children between 2 and 11 years of age. *Br J Clin Pharmacol*. 2007;63(5):534-540. doi:10.1111/j.1365-2125.2006.02810.x
149. Gupta SK, Kantesaria B, Banfield C, Wang Z. Desloratadine dose selection in children aged 6 months to 2 years: comparison of population pharmacokinetics between children and adults. *Br J Clin Pharmacol*. 2007;64(2):174-184. doi:10.1111/j.1365-2125.2007.02859.x
150. Meltzer EO, Scheinmann P, Rosado Pinto JE, et al. Safety and efficacy of oral fexofenadine in children with seasonal allergic rhinitis–a pooled analysis of three studies. *Pediatr Allergy Immunol*. 2004;15(3):253-260. doi:10.1111/j.1399-3038.2004.00167.x
151. Pampura AN, Papadopoulos NG, Spicak V, Kurzawa R. Evidence for clinical safety, efficacy, and parent and physician perceptions of levocetirizine for the treatment of children with allergic disease. *Int Arch Allergy Immunol*. 2011;155(4):367-378. doi:10.1159/000321181
152. Potter P, Mitha E, Barkai L, et al. Rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2–11 years. *Pediatr Allergy Immunol*. 2016;27(1):55-61. doi:10.1111/pai.12460
153. Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy. A prospective observational cohort study. *Reprod Toxicol*. 2008;26(1):19-23. doi:10.1016/j.reprotox.2008.05.053
154. Schwarz EB, Moretti M, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis. *Drug Saf* 2008;31(9):775-788.
155. Namazy J, Cabana MD, Scheuerle AE, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. *J Allergy Clin Immunol*. 2015;135(2):407-412. doi:10.1016/j.jaci.2014.08.025
156. González-Medina M, Curto-Barredo L, Labrador-Horrillo M, Giménez-Arnau A. Omalizumab use during pregnancy for chronic spontaneous urticaria (CSU): report of two cases. *J Eur Acad Dermatol Venereol*. 2017;31(5).
157. Ghazanfar MN, Thomsen SF. Successful and safe treatment of chronic spontaneous urticaria with omalizumab in a woman during two consecutive pregnancies. *Case Rep Med* 2015;2015:1-3. doi:10.1155/2015/368053
158. Ensina LF, Cusato-Ensina AP, Camelo-Nunes IC, Solé D. Omalizumab as third-line therapy for urticaria during pregnancy. *J Investig Allergol Clin Immunol*. 2017;27(5):326-327. doi:10.18176/jiaci.0179
159. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406. doi:10.1016/j.jclinepi.2010.07.015
160. Maurer M. Cold Urticaria. In Saini SS, Callen J, eds. *UpToDate*. Wolters Kluwer Health; 2014.

How to cite this article: Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77:734–766. doi:10.1111/all.15090