Methods Report

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

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NOTES ON USE/DISCLAIMER

This is the Methods Report for the International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria.[1] Because the 2021 guideline is an update and revision of the EAACI/GA²LEN/EDF/WAO guideline on urticaria published in 2018,[2] some parts of this Methods Report will be identical or similar in wording to the previous methods report published in 2018.[3] Some of the wording will also be identical or similar to that in the methods section of the main guideline document,[1] which itself is a summary of the present Methods Report.

FUNDING

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria 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. All of these organisations provided funding for the development of the guideline. There was no funding from other sources. The funders were not involved in the analysis of data or the writing of the Methods Report and the Evidence Report.

INTRODUCTION

This report presents the methods and processes used to develop the It also presents the evidence identified and generated through the systematic literature review and meta-analysis that underpin the recommendations of the expert panel. The guideline should be referenced as:

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. 2021;00:1–33. doi:10.1111/all.15090

The EuroGuiDerm staff at the Division of Evidence-Based Medicine, Department of Dermatology, Venereology and Allergy, Charité – Universitätsmedizin Berlin conducted the evidence assessment, prepared the evidence-to-decision frameworks, facilitated the online voting, and co-prepared and co-facilitated the consensus conference.

INVOLVING STAKEHOLDERS AND FORMING THE GUIDELINE SUBCOMMITTEE

An email invitation to nominate experts to participate in the development of the guideline was sent to all relevant national societies by Remember Management[1]. The EuroGuiDerm team additionally asked those societies that contribute financially to EuroGuiDerm and that had not been involved in the development of the 2017 version of the guideline to nominate an expert as well (Finland, Hungary, Malta, Belgium, Norway and Greece). The funding society in Greece declined, and there was no reply

[1] Remember Management is a private company responsible for the organisation of the hybrid conference. Otherwise they were not involved.

from those in Belgium or Norway. Additionally, an open call went out to all EDF members and was circulated via social media/newsletters. For the list of interdisciplinary experts and their countries, nominating societies, affiliation/specialties, see Table 1; for the members of the EuroGuidDerm methodologist group, see Table 2.

TABLE 1: MEMBERS OF THE EXPERT PANEL

Title	First name	Last name	Country	Nominating society	Affiliations/specialties
Dr.	Amir Hamzah	Abdul Latiff	Malaysia	Malaysian Society of Allergy and Immunology (MSAI)	Allergy & Immunology Centre, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
Dr.	Mohamad	Abuzakouk	United Arab Emirates	Pan-Arab Society of Allergy and Immunology (PASAAI)	Department of Allergy and Immunology, Respiratory Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
Dr.	Susan	Aquilina	Malta	Maltese Association of Dermatology & Venereology (MADV)	Department of Dermatology, Mater Dei Hospital, Msida, Malta
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
Dr.	Diane R.	Baker	USA	American Academy of Dermatology (AAD)	Baker Allergy, Asthma and Dermatology, Portland, Oregon, USA
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
Dr.	Christine	Bangert	Austria	Austrian Society of Dermatology and Venereology (ÖGDV)	Department of Dermatology, Medical University of Vienna, Vienna, Austria
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
Prof. Dr.	Jonathan A.	Bernstein	USA	American Academy of Allergy Asthma & Immunology (AAAAI)	University of Cincinnati Physicians Immunology Research Center, Cincinnati, OH, USA
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
Prof. Dr.	Knut	Brockow	Germany	German Society of Dermatology (DDG)	Department of Dermatology and Allergy Biederstein, Faculty of Medicine, Technical University Munich, Munich, Germany
Dr.	Zenon	Brzoza	Poland	Polish Society of Allergology (PTA)	Department of Internal Diseases with Division of Allergology,

					University of Opole, Opole, Poland
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
Prof. Dr.	Martin K.	Church	UK	Global Allergy and Asthma European Network (GA²LEN)	Charité-Universitätsmedizin Berlin, Germany, University of Southampton, UK
Dr.	Paulo Ricardo	Criado	Brazil	Brazilian Society of Dermatology (SBD)	Sociedade Brasileira de Dermatologia (SBD), Centro Universitário FMABC, Alergoskin (UCARE), Brazil
Dr.	Inna Vladimirov-na	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
Dr.	Luis Felipe	Ensina	Brazil	Brazilian Society of Allergy and Immunology (ASBAI)	Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil
Prof. Dr.	Luz	Fonacier	USA	American College of Allergy, Asthma and Immunology (ACAAI)	New York University Long Island School of Medicine, New York, USA
Dr.	Krisztián	Gáspár	Hungary	Hungarian Dermatological Society (MDT)	Division of Dermatological Allergology, Department of Dermatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
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
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
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
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
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

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
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
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
Prof. Dr.	Michihiro	Hide	Japan	Japanese Dermatological Association (JDA)	Department of Dermatology, Hiroshima University, Hiroshima, Japan (Current affiliation: Department of Dermatology, Hiroshima Citizens Hospital, Hiroshima, Japan)
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
Prof. Dr.	Alexander	Kapp	Germany	Deutsche Akademie für Allergologie und Umweltmedizin (DAAU)	Department of Dermatology & Allergy, Hannover Medical School (MHH), Hannover, Germany
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
Dr.	Emek	Kocatürk	Turkey	Turkish Society of Dermatology (TDD)	Department of Dermatology, Koç University School of Medicine, Istanbul, Turkey
Prof. Dr.	Kanokvalai	Kulthanan	Thailand	Dermatological Society of Thailand (DST)	Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
Dr.	Désirée	Larenas-Linnemann	Mexico	Global Allergy and Asthma European Network (GA²LEN)	Hospital Médica Sur, Mexico City, Mexico
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
Dr.	Tabi	Leslie	UK	British Association of Dermatologists (BAD)	Department of Dermatology, Royal Free Hospital, London, UK
Prof. Dr.	Markus	Magerl	Germany	Urtikaria Netzwerk Berlin Brandenburg (UNBB)	Dermatological Allergology, Allergie-Centrum-Charité, 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; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany
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
Prof. Dr.	Marcus	Maurer (guideline co-coordinator, co-author)	Germany	European Academy of Allergy and Clinical Immunology (EAACI)	Dermatological Allergology, Allergie-Centrum-Charité, 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; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany
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
Prof. Dr.	Martin	Metz	Germany	European Mast Cell and Basophil Research Network (EMBRN)	Dermatological Allergology, Allergie-Centrum-Charité, 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; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany
Dr.	Daniel	Micallef	Malta	Maltese Association of Dermatology & Venereology (MADV)	Department of Dermatology, Mater Dei Hospital, Msida, Malta
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Dr.	Hanneke	Oude-Elberink	Netherlands	Dutch Society of Allergology (NVvA)	University of Groningen, Groningen, The Netherlands
Prof. Dr.	Ruby	Pawankar	India	Asia Pacific Association of Allergy, Asthma and	Department of Pediatrics, Nippon Medical School, Tokyo, Japan

				Clinical Immunology (APAAACI)	
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
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
Dr.	María Isabel	Rojo Gutiérrez	Mexico	Mexican College of Clinical Immunology and Allergy (CMICA)	Hospital Juárez de México, Mexico City, Mexico
Dr.	Sarbjit (Romi)	Saini	USA	American Academy of Allergy Asthma & Immunology (AAAAI), World Allergy Organization (WAO)	Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA
Prof. Dr.	Peter	Schmid-Grendelmeier	Switzerland	Swiss Society of Dermatology and Venereology (SGDV)	Allergy Unit, Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland
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
Dr.	Frank	Siebenhaar	Germany	European Mast Cell and Basophil Research Network (EMBRN)	Dermatological Allergology, Allergie-Centrum-Charité, 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; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology, Berlin, Germany
Dr.	Hanna	Siiskonen	Finland	Finnish Dermatological Society (FDS)	Department of Pathology, Diagnostic Imaging Centre, Kuopio University Hospital, Kuopio, Finland
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
Prof. Dr.	Petra	Staubach-Renz	Germany	Urticaria network (patient organization) (UNEV)	Department of Dermatology, University Medical Center Mainz, Mainz, Germany
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

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
Prof. Dr.	Andrea	Szegedi	Hungary	Hungarian Dermatological Society (MDT)	Division of Dermatological Allergology, Department of Dermatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
Prof. Dr.	Simon Francis	Thomsen	Denmark	Danish Dermatological Society (DDS)	Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark
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
Dr.	Christian	Vestergaard	Denmark	Danish Dermatological Society (DDS)	Department of Dermatology and Venereology, Aarhus University Hospital, Aarhus, Denmark
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
Prof. Dr.	Zuotao	Zhao	China	Chinese Dermatologist Association (CDA)	Department of Dermatology and Venereology, Peking University First Hospital, Beijing, China
Prof. Dr.	Torsten	Zuberbier (guideline co-coordinator, co-author)	Germany	European Dermatology Forum (EDF)	Dermatological Allergology, Allergie-Centrum-Charité, 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

TABLE 2: MEMBERS OF THE EUROGUIDERM GUIDELINE METHODOLOGY GROUP

Title	First name	Last name	Country	Organisation	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

DECLARATION AND MANAGEMENT OF CONFLICTS OF INTEREST

All nominated experts 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). Experts were asked to self-declare their interests via the online tool "*Declaration of Interests for EuroGuiDerm Guidelines".* An overview of the declarations of personal-financial conflicts of interests is given in Table 3. In total, 40 declared that they had no P-F COI (62.5%).

TABLE 3: DECLARATIONS OF PERSONAL-FINANCIAL CONFLICTS OF INTERESTS AS PROVIDED BY THE EXPERTS

Title	First name	Last name	As declared by the person:
Dr.	Mohamad	Abuzakouk	No
Dr.	Sue	Aquilina	No
Prof. Dr.	Riccardo	Asero	No
Dr.	Diane	Baker	No
Prof. Dr.	Barbara	Ballmer-Weber	Speaker fees and honorarium for advisory boards from Novartis
Dr.	Christine	Bangert	Advisory board participation (Novartis) Lectures (Novartis)
Dr.	Moshe	Ben-Shoshan	Consultant Novartis (up to 3000 cad a year)
Prof. Dr.	Jonathan A.	Bernstein	Shire/Takeda, CSL Behring, Pharming, Kalvista, Ionis, Biocryst, Novartis, Genentech, Sanofi Regeneron, Astra Zeneca
Prof. Dr.	Carsten	Bindslev-Jensen	No
Dr.	Knut	Brockow	No
Dr.	Zenon	Brzoza	No
Prof. Dr.	Herberto José	Chong Neto	No
Prof. Dr.	Martin K.	Church	No
Dr.	Paulo Ricardo	Criado	Speaker Novartis SA and Takeda
Dr.	Inna Vladimirovna	Danilycheva	No
Dr.	Luis Felipe	Ensina	Received personal fees as speaker and consultant from Novartis and Takeda
Prof. Dr.	Luz	Fonacier	Honoraria Sanofi
Dr.	Krisztián	Gáspár	No
Prof. Dr.	Aslı	Gelincik	No
Prof. Dr.	Ana	Giménez-Arnau	Medical Advisor for Uriach Pharma, Genentech, Novartis, FAES, GSK, Sanofi–Regeneron, Amgen, Thermo Fisher Scientific , Almirall , LEO-Pharma; research Grants supported by Uriach Pharma, Novartis, Grants from Instituto Carlos III- FEDER; educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO-PHARMA, GSK, MSD, Almirall, Sanofi
Prof. Dr.	Kiran	Godse	No
Prof. Dr.	Margarida	Gonçalo	Has received fees for advisory boards and teaching from Novartis and Sanofi, Genzyme
Dr.	Clive	Grattan	Consultancy Celltrion
Dr.	Martine	Grosber	No
Prof. Dr.	Eckard	Hamelmann	No

Dr.	Jacques	Hébert	Adboard and speaker fees for Novartis
Prof. Dr.	Michihiro	Hide	Honorarium from Kaken, Kyowahakko-Kirin, Mitsubishi-Tanabe, Novartis, Sanofi, Taihoyakuhi, Teikokuseiyaku and Uriach.
Prof. Dr.	Allen	Kaplan	Adjudication committee for allergic reactions and anaphylaxis--Novartis/Genentech
Prof.Dr.	Alexander	Kapp	Some Novartis shares
Prof. Dr.	Aharon	Kessel	No
Dr.	Emek	Kocatürk	Specific financial personal Novartis (honorary for giving lectures and advisory board fees)
Prof. Dr.	Kanokvalai	Kulthanan	Received honoraria for educational lectures from Menarini.
Dr.	Désirée	Larenas-Linnemann	None directly. Indirectly: Lecturer/adboard member/grants: Novartis, Sanofi, GSK, Astrazeneca, Mylan/Viatris, Menarini, Siegfried Mexico, Amstrong, Abvvie, Bayer, Pfizer, DBV Technologies, Merck-Sharp-Dohme Mexico, Purina institute, Alakos, Carnot.
Dr.	Amir H. Abdul	Latiff	No
Prof. Dr.	Antti	Lauerma	No
Dr.	Tabi	Leslie	Novartis
Prof. Dr.	Markus	Magerl	Honoraria from Novartis (speaker)
Dr.	Michael	Makris	Primary investigator in CQGE031C2302 study (Phase 3, Novartis) in "Attikon" Allergy Unit Study Centre
Prof. Dr.	Marcus	Maurer	Is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Alnylam, Aralez, AstraZeneca, FAES, Genentech, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, UCB, and Uriach.
Prof.	Raisa Yakovlevna	Meshkova	No
Prof. Dr.	Martin	Metz	Received honoraria as a speaker for Aralez, Novartis, Roche, Uriach I have received honoraria as a consultant for Amgen, argenx, Moxie, Novartis
Dr.	Daniel	Micallef	No
Prof. Dr.	Charlotte G	Mortz	No
Dr.	Hanneke	Oude-Elberink	No
Prof.	Ruby	Pawankar	No
Prof. Dr.	Paolo	Pigatto	No
Prof. Dr.	Héctor	Ratti Sisa	No
Dr.	María Isabel	Rojo Gutiérrez	No
Dr.	Sarbjit (Romi)	Saini	No
Prof. Dr.	Peter	Schmid-Grendelmeier	Speaker fees and honararium for sdvisory boards from Novartis Pharma and Roche Pharma
Prof. Dr.	Bulent Enis	Sekerel	No
Dr.	Frank	Siebenhaar	No
Dr.	Hanna	Siiskonen	No
Prof. Dr.	Angèle	Soria	Personal Financial Interest for consulting: Novartis Pharma
Prof. Dr.	Petra	Staubach-Renz	No
Prof. Dr.	Luca	Stingeni	No
Dr.	Gordon	Sussman	Advisory board member: Novartis, Aralez, CSL Behring, Sanofi Received grant or honorarium: Novartis, Aralez, Pediapharm, GSK, Genentech, DBV technologies, Aimmune, CSL Behring, Astrazeneca, Stallergenes, Merck, Pfizer, Dyax, Biocryst, Greencross, Kendrion, Shire, Leopharma, Regeneron,

			mdBriefCase. Currently participating or have participated in clinical trial (PI): Novartis, GSK, Genentech, DBV technologies, Aimmune, CSL Behring, Astrazeneca, Stallergenes, Merck, Pfizer, Dyax, Biocryst, Greencross, Kendrion, Leo Pharma, Regeneron, Sanofi, Blueprint, ALK, Amgen, Cliantha.
Prof. Dr.	Andrea	Szegedi	No
Prof. Dr.	Simon Francis	Thomsen	No
Prof. Dr.	Zahava	Vadasz	No
Dr.	Christian	Vestergaard	No
Prof. Dr.	Bettina	Wedi	Personal honoraria for educational lectures and one-day advisory boards of Novartis Pharma GmbH; PI in several RCTs sponsored by Novartis Pharma GmbH with payments to my organization (university hospital).
	Zuotao	Zhao	No
Prof. Dr.	Torsten	Zuberbier	Industry Consulting or honoraria: AstraZeneca, AbbVie, ALK, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES, HAL, Henkel, Kryolan, Leti, L'Oreal, Meda, Menarini, Merck, MSD, Novartis, Pfizer, Sanofi, Stallergenes, Takeda, Teva, UCB

For a list of participants in the consensus conference and their declarations of personal-financial conflicts of interests, please contact EuroGuiDerm at debm.de. Only those working for a pharmaceutical company were excluded from voting during the consensus conference.

METHODS

SCOPING AND DEFINING THE PURPOSE OF THE GUIDELINE

The EuroGuiDerm staff (CD) prepared a scoping document in line with the requirements of the EuroGuiDerm Methods Manual. The draft was sent to EDF members and the EuroGuiDerm Board of Directors on 20 May 2020 for commenting, and comments were taken into consideration.

The aim of the guideline is to provide a definition and classification of urticaria, thereby facilitating the interpretation of divergent data from different centres and areas of the world regarding underlying causes, eliciting factors, 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.

SELECTING AND SPECIFYING GUIDELINE QUESTIONS

See the Methods Report[3] of the previous guideline update for details on the processes used in 2016 to (a) suggest an initial list of key questions for that update of the guideline, as well as to (b) have the expert panel vote on whether to include or exclude key questions from this initial list and (c) choose relevant outcomes a priori and have the expert panel rate these in terms of their importance.

For the 2020 update of the guideline, the guideline coordinators decided that the same key question would be used. Those can be found in the guideline itself.

SEARCH METHODS, SEARCH RESULTS AND EVIDENCE SELECTION

SEARCH

The key questions had been translated in the PICO format, which specifies the intervention, comparison and outcome used to assess efficacy and safety (see box 1). PICO is specified in the header of each evidence-to-decision framework. Systematic searches for randomized controlled trials and clinical, controlled trials were undertaken using the following databases on 15 May 2020 limiting the time to 2016 – 15 May 2020:

- Ovid MEDLINE(R) ALL 1946 to May 14, 2020
- Embase Classic+Embase 1947 to 2020 May 14
- Cochrane Central Register of Controlled Trials (CENTRAL)

All search strategies can be found in Appendix 1: Search Strategies. We did not search trials registries, grey literature sources, or contact authors due to resource limitations. EndNote X9™ was used to manage references.

Because the Update of the EAACI/GA²LEN/EuroGuiDerm/APAAACI International Guideline for Urticaria is an update of an existing guideline,, we did not search for other guidelines or systematic reviews.

ELIGIBILITY CRITERIA

The pre-selected inclusion criteria for the title/abstract and full-text screening are given in Box 1. The exclusion criteria for the title/abstract and full-text screening are given in Box 2.

BOX 1: PICO / INCLUSION CRITERIA

Population

Patients of all ages and genders with:

- chronic spontaneous urticaria (CSU) (a.k.a. chronic idiopathic/chronic urticaria)
- chronic inducible urticaria (CindU) (i.e. cold urticaria, pressure urticaria, heat urticaria, solar urticaria, symptomatic dermographism (=urticaria factitia), vibratory angioedema, aquagenic urticaria, cholinergic urticaria, contact urticaria)
- angioedema without wheal

Interventions (stated with minimum standard dosage for adults, where applicable)

H1-antihistamines (H1-AH) 1st generation:

- clemastine fumarate 1mg BID (≙ 1.34mg clemastin fumarate), 20ml sirup BID (≙ 1.34mg clemastine hydrogen fumarate = 1mg clemastine); dimetindene maleate 0.05-0.1mg/kg BW QD (≙ 1-2 dragees à 1mg dimetindene maleate), 1ml TID (≙ 20 drops); diphenhydramine; hydroxycine dihydrochloride 37.5mg (≙ 1,5 tablets; 25mg ≙ 20.93mg hydroxycine); ketotifen fumarate (HC 20-511 Sandoz) 1.38mg (≙ 1 capsule)

H1-antihistamines 2nd generation:

- acrivastin 8mg TID; bilastine 20mg QD (≙ 1 tablet); cetirizine dihydrochloride 10mg QD (≙ 1 tablet ≙ 8.42mg cetirizine)/ 10mg sirup QD (1ml sirup ≙ 1mg cetirizin-$_2$HCl); desloratadine 5mg QD (≙ 1 tablet); ebastine 10mg QD (≙ 1 tablet); emedastine 2mg BID (≙ 1 drop BID; 1ml solution ≙ 0.5mg emedastine [0.05%] as difumarate [0.884mg/1ml emedastine difumarate]); fexofenadine 180mg QD (≙ 1 tablet); levocetirizine dihydrochloride 5mg QD (≙ 1 tablet ≙ 4.2mg levocetirizine); loratadine 10mg QD (≙ 1 tablet); mizolastine 10mg QD (≙ 1 tablet); rupatadine 10mg QD (≙ 1 tablet ≙ 12.79mg rupatadine fumarate)

Other therapies:

- anakinra (100mg) in 0.67ml (150 mg/ml) syringe; autologous whole blood (AWB)/ autologous serum/ autohemotherapy; colchicine; cyclosporine; dapsone; doxepine 50mg QD (≙ 5 tablets; 1 tablet ≙ 11.31mg rupatadine fumarate); heparin; hydroxychloroquine; intravenous immunoglobulins (IVIG); methotrexate; montelukast 10mg (≙ 10.38mg montelukast sodium); omalizumab 150mg and 300mg per month (100mg omalizumab ≙ 1ml solution in syringe); oral corticosteroids (prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone); phototherapy: UVB, narrow band-UVB, PUVA; rituximab (50ml contain 500mg rituximab [CHO-cells]); sulfasalazine; tacrolimus; TNF-alpha inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab

Comparisons

- 2nd generation H1-AH vs. placebo
- 2nd generation H1-AH vs. 1st generation H1-AH
- Low dose 2nd generation H1-AH vs. high-dose 2nd generation H1-AH (up to 4-fold)
- H1- AH vs. other therapies
- H1-AH vs. H1-AH combined with other therapies (other therapies refers to those listed above)
- Other therapies vs. each other (other therapies refers to those listed above)

Outcomes

- Proportion of participants with complete suppression of urticaria
- Proportion of participants with 'good' or 'excellent' response
- Proportion of participants with 50% or greater improvement in quality of life measurements
- Mean reduction in Weekly Urticaria Activity Score (UAS7)
- Serious adverse events (i.e. serious enough to require withdrawal of treatment)
- Proportion of participants who relapse within one month of stopping intervention
- Minor participant-reported adverse events not requiring withdrawal of treatment, e.g. sedation

Study types

- Randomised controlled trials
- Controlled clinical trials (defined as a clinical studies that includes a comparison group)

BOX 2: EXCLUSION CRITERIA

- healthy volunteers with induced wheals
- urticaria pigmentosa
- food-induced allergic reaction, for example, shrimp allergy
- hereditary angioneurotic edema/ hereditary angioedema (HAE)
- contact urticaria
- diets other than as defined as pseudoallergene diet
- studies reporting outcomes at a follow-up time of more than 12 weeks only
- outcome assessment after a treatment duration shorter than 1 week
- comparisons of same medication in different treatment regime (for example verum A updosing every week versus verum B updosing every week,) or different applications (for example, tablet versus capsule)
- if only an abstract was available and no numerical data for efficacy outcomes (only p-values or text) were reported, the abstract was excluded
- if in the full-text publication (including any supplementary materials) numerical outcome data were not provided in a format suitable for ReviewManager, the full-text was excluded (for details, see section Statistical Analysis).

SCREENING AND DATA EXTRACTION

Two researchers (AN, MG) independently screened the titles and abstracts of all hits for eligibility. In cases where no abstract was available and the title did not give an obvious reason for exclusion, we obtained the full-text publication. The two researchers subsequently screened the full-text publications of the included titles and abstracts for eligibility. In some cases, only abstracts were available; we included these if they met our eligibility criteria.

Data were then extracted from the included publications by the two researchers independently of each other using a standardized data extraction form in MS Excel. These were subsequently compared and differences of opinion were resolved by discussion. The items listed in Table 4 were extracted if available in the pre-defined format. Data were transformed whenever appropriate (see below). We used Engauge Digitizer Version 4.7 to extract data points from images of graphs.

TABLE 4: ITEMS FOR DATA EXTRACTION

Study characteristics and baseline data	
First author and year	First author and year of print publication
Intervention	Latin abbreviation for treatment regimen; duration of treatment as stated in publication; PBO for matched placebo and 'nothing' for no medication
Randomized or assigned patients	n (number of patients per arm)
Study design	Type of RCT or CCT, multi-centre (MC) or single-centre (SC)
Inclusion criteria disease	CIU, CSU, CU or CIndU type; extraction of full inclusion criteria from study
Inclusion criteria age	Years (as stated)
Special patient population	No; children (age), pregnant or lactating women
Washout	Duration and medication
Concomitant treatment	As stated in publication
Age at baseline	Mean±SD, median (IQR), or range (as reported in publication)
Gender distribution at baseline (female)	% (rounded off to whole numbers)
Outcomes: efficacy and HRQL data are extracted for week 1-2 and week 3 – 12	
Follow-up point in time	As stated in publication

Definition of outcome (scoring)	As stated in publication - *must be investigator assessed*
Matched outcome	State score that was matched with 'complete suppression'
Patients with complete suppression	n/N
Matched outcome	State score that was matched with 'good' or 'excellent'
Patients with at least 'good' or 'excellent' response	n/N (includes n of complete suppression)
Follow-up point in time	As stated in publication
Definition of efficacy score	As stated in publication
Mean change (SD)	Mean±SD and n / *make note of who assessed*
Follow-up point in time	As stated in publication
UAS or UAS7	state which one: UAS or UAS7 */make note of who assessed it*
Patients with ≤ 6 points	n/N
Follow-up point in time	As stated in publication
Definition of HRQL outcome	As stated in publication
Mean change (SD)	Mean±SD and n
Patients with ≥50% improvement in QoL	n/N
Outcomes: Adverse events and Relapse	
Withdrawal/drop out due to adverse event	n/N
Point in time of adverse event	As stated in publication
Patients with at least 1 adverse event	n/N
Adverse Events	Number of patients with somnolence, fatigue, drowsiness, tiredness, dizziness *for studies comparing 1st vs. 2nd gen AH only (preferable 'patient-assessed')*
Definition of relapse	Definition of relapse at time x (up to max. 6 months)
Proportion of patients relapsing at time x	n/N

Notes: CCT: controlled clinical trial; CindU: chronic inducible urticaria; CIU: chronic idiopathic urticaria; CSU: chronic spontaneous urticaria; CU: chronic urticaria; IQR: interquartile range; QoL: quality of life; RCT: randomised controlled trial; SD: standard deviation; UAS: urticaria activity score; UAS7: seven-day urticaria activity score

STATISTICAL ANALYSIS

This section is, in large part, identical to that in the previous Methods and Evidence Report[3]

We calculated risk ratios and mean differences with the corresponding 95% confidence intervals using Review Manager 5.4.[4] Each comparison and outcome were entered into Review Manager separately, and subgroups for each point in time of evaluation were created. We included several multi-arm studies where the comparator arm was split in case of multiple comparisons to avoid counting participants more than once (only when data were later pooled). The methods offered by Review Manager are not ideal for analysing rare events (e.g., number of/proportion of patients, who experiences an adverse event). A zero-cell correction is applied or an estimation is not possible when events are zero in both groups; other statistical methods offer options, but are advanced and present own drawbacks.[5-7] Hence, we decided to calculate the risk difference instead of the risk ratio in some cases.

Decisions on appropriateness of pooling the data were made taking the PICO and the key question into consideration. We choose the Mantel-Haentzel approach using a random-effects model because the difference between the studies suggested that no common effect was assessed (DerSimionian-Laird).[8] The decision was made to pool data if heterogeneity was I^2 <= 80%. In cases were I^2 >= 40%, we downgraded during the assessment of the quality of evidence (GRADE – inconsistency criteria).

We pooled data across time points: week 1 and 2, week 3 and 4 and across week 5 and 6. Data were not pooled across 8 and 12 weeks or when the dosage changed between two time points. If multiple time points had been reported, we preferred the earliest time point in each time bracket.

Due to the different assessment scales used, we calculated an SMD where this was more appropriate.

DATA TRANSFORMATION

We performed a variety of data transformations because the data reported in the included publications were not always in a format suitable for meta-analysis.

$$SD_{E,\,change} = \sqrt{SD^2_{E,\,baseline} + SD^2_{E,final} - (2 \times Corr \times SD_{E,\,basline} \times SD_{E,\,final})}$$

$$Corr_E = \frac{SD^2_{E,baseline} + SD^2_{E,final} - SD^2_{E,change}}{2 \times SD_{E,baseline} \times SD_{E,final}}$$

In order to calculate summary measures for continuous outcomes, a measure of dispersion, i.e. the standard error or the standard deviation (SD) had to be available. For continuous outcomes the absolute mean change in a score from baseline could be calculated where baseline and final data were provided. The corresponding standard deviation could only be calculated using the formula below if we were able to use data from another publication and calculate a correlation coefficient assuming that the intervention did not change the variability of the outcome measures, as suggested by Cochrane.[9]

Otherwise missing standard deviations for mean changes were calculated based on the confidence interval and the standard error. If only the baseline mean value ± SD and the end mean value without SD (i.e., was digitised from a chart) was available or the final mean ± SD but no SD for the mean change was reported or calculable, no effect measure could be calculated. Concerning dichotomous efficacy outcomes, we calculated a non-responder-imputation-based ITT to harmonize the data pool.

$$SE = (\text{upper limit CI} - \text{lower limit CI}) / 3.92$$

$$SD = SE \times \sqrt{N}$$

Mean change was always preferred, but if not available or the above calculations were not possible, we pooled the final mean and mean change.

CRITICAL APPRAISAL OF EVIDENCE

RISK OF BIAS ASSESSMENT

The data extraction sheet also contained the categories of the Cochrane Risk of Bias Assessment Tool ,[10] which we used to assess *sequence generation*, *allocation concealment* and *other sources of bias* at the study level, and *blinding of patients and personnel* and *blinding of outcome assessment* at the outcome level. For the specific decision-making criteria used to make the assessments, please refer to the

previous Methods and Evidence Report.[3] We used the ROBINS – I tool for non-randomized clinical controlled trials.[11]

GRADE ASSESSMENT OF THE QUALITY OF EVIDENCE

The GRADE approach was used to appraise the quality of evidence and develop evidence-to-decision frameworks.[12] We used the online application GRADE pro GDT[13] to create GRADE evidence profiles for each comparison. During this process, the following five criteria were used to rate each outcome as *not serious*, *serious* (downgraded by 1 level) or *very serious* (downgraded by 2 levels). Randomized, controlled trials (RCT) start with the highest rating (not serious). A summary of the criteria influencing the quality and the different quality levels are displayed in Table 5 (adapted from Bashem et al. 2001[14]). Each criterion that may decrease the quality rating is described in detail below.

TABLE 5: SUMMARY OF THE GRADE APPROACH TO ASSESSING THE QUALITY OF EVIDENCE BY OUTCOME IN RANDOMISED CONTROLLED TRIALS[14]

Initial 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.

1. Risk of bias: The Cochrane Risk of Bias Assessment tool was used. We downgraded if several risk of bias items were deemed unclear and/or high. Where more than one study had been included in a meta-analysis, we looked at the weights assigned in the meta-analysis to help determine the overall risk of bias.

2. Inconsistency: If only one study was available, we could not assess inconsistency. No default option for this case is available; hence, we rated inconsistency as *not serious.* If more than one study was

included, we downgraded to *serious* if statistical heterogeneity was detected as $I^2 \geq 40\%$ and to *very serious* if $I^2 \geq 70\%$.

3. *Indirectness*: Only if the population and/or intervention specified in the key question differed from the population and/or intervention in the studies included did we downgrade to *serious*. For example, if a study included non-responders to different doses of H1-AH but the PICO question had specified for the population to be non-responder to high doses of H1-AH did we downgrade.

4. Imprecision: Imprecision was rated as *serious* if the confidence interval was very wide (for example, 0.06 to 15.14 or 2.05 to 97.04). In addition, the boundaries of the calculated confidence intervals were assessed. The GRADE approach postulates for the minimal clinical important difference (MID) thresholds to be larger than 25% benefit (1.25) and 25% harm (0.75).[14] If the confidence interval crossed the MID threshold this represents uncertainty in regards to clinical importance. If one or both MID thresholds were crossed, we downgraded to *serious*. If only the line of no effect was crossed but no MID threshold, we did not downgrade because the result is precise.

For continuous outcomes, we based our assessment on MID thresholds that are anchor-based and available in the peer-reviewed literature. For the Dermatology Quality of Life Index with a possible range of scores from 0 to 30, the MID threshold used was 3 (Shikiar et al. 2005 suggested 2.2 to 3.2; [15]). For the Urticaria Activity Score 7 (UAS7) Mathias et al. 2012 had suggested an MID range from 9.5 to 10.5, we used 10.[16] In cases where we calculated the risk difference for rare events (for example for AEs), we used a 2% as the MID. When we used the SMD, we used - 0.2 / 0.2 (as small effect, see Cohen).

Where no anchor-based MIDs were available, we used distribution-based MIDs, namely ½ the SD.[17] We did not downgrade the quality rating for imprecision in the case of zero events.

5. Publication bias: Due to the small number of studies whose data were pooled for most comparisons, we were unable to assess publication bias, for example, using a funnel plot and rated this form of bias as 'undetected'.

Just as we used each PICO question to create a GRADE evidence profile (or set of such profiles), so too did we use each GRADE evidence profile to develop an Evidence-to-Decision (EtD) framework. These aimed to help the members of the expert panel (a) make an overall judgement regarding the size of the desirable and undesirable effects of specific comparisons and the balance between the two, (b) summarize the overall quality of the evidence, and (c), in doing so, develop the evidence- and consensus-based guideline recommendations and accompanying background texts.

RESULTS OF THE EVIDENCE UPDATE

The literature search on 15 May 2020 identified 2053 records. The removal of duplicates left 1602 records for the title/abstract screening, of which 1458 were excluded. This left 144 records to be assessed as full texts for eligibility, of which 123 were excluded. A list of excluded full-text publications with reasons for exclusion can be found in Appendix 2. A total of 21 records were ultimately included in the evidence-based review. These comprised (a) 13 new studies reporting data on treatments for CSU

and two studies reporting additional data to that included in the 2017 guideline and (b) two new studies reporting data on treatments for CINDU and one study reporting additional data to that included in the 2017 guideline. Of the former group, one study was excluded at the data extraction stage because it did not report the requisite dispersion measures.[18] A breakdown of this process can be seen in the study selection flowchart in Figure 1. Additionally, in the EtD frameworks, an asterisk (*) after an author-year reference or a particular outcome indicates where new data were identified or added to existing data as part of the 2020/21 update or the guideline.

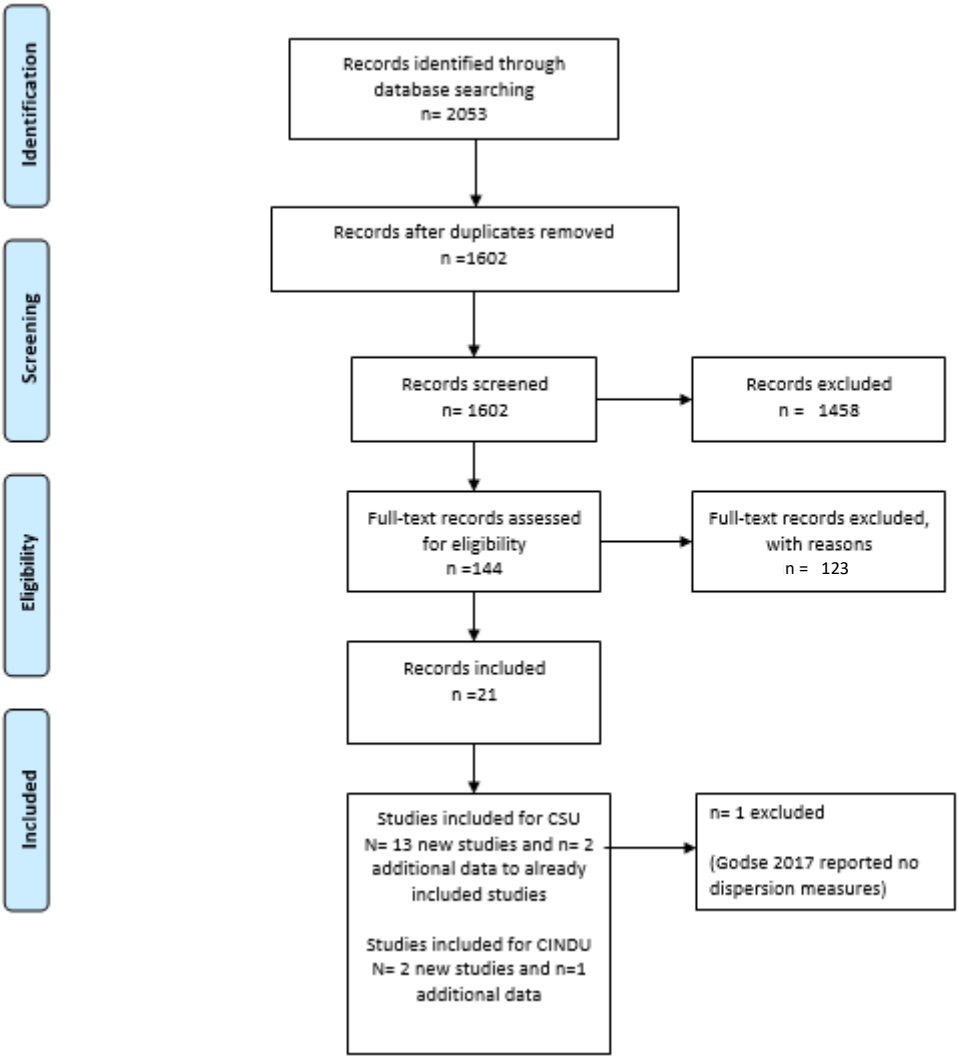

FIGURE 1. STUDY SELECTION FLOWCHART

We created a total of 14 new or updated GRADE evidence profiles and 14 new or updated EtD frameworks. A summary of the evidence is given in the Evidence Report, which is available on the EDF website (https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html).

DEVELOPING RECOMMENDATIONS AND THE CONSENSUS PROCESS

When developing the guideline recommendations, the expert panel always used the standardized wording suggested by the GRADE Working Group and in accordance with the EuroGuiDerm Manual (see Table 6).[19]

TABLE 6: WORDING OF RECOMMENDATIONS[20-23]

Strength	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 health care 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 (for example, 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.

At the beginning of the guideline development process, the guideline co-coordinators (MM and TZ) divided the expert panel into two groups of roughly equal size. One group was chiefly responsible for the guideline sections on classification and diagnosis, which were developed based on expert consensus, and the other group was chiefly responsible for the guideline sections on disease management, most of which were developed based on the results of our systematic search of the literature and meta-analysis of data from the included studies.

Members of the classification and diagnosis group were instructed to write draft recommendations based on their clinical expertise and expert consensus within group while drawing as necessary upon relevant literature. In turn, members of the disease management group, were instructed to write draft

recommendations based on the GRADE profiles and EtD frameworks we supplied to them as part of our Evidence Report, and on their clinical expertise within the subgroup. The guideline coordinators helped coordinate this process.

We conducted two online surveys, each among all the members of the expert panel, in the weeks before the consensus conference on 3 December 2020 in order to (a) familiarise the group with all of the draft recommendations, (b) gather feedback from the group on the these recommendations and (c) subsequently use this feedback to modify the recommendations or to draft alternatives to them to be presented and voted upon during the consensus conference on 3 December 2020.

The first online survey focused on the diagnosis and classification section of the guideline. The survey began on 25 August 2020 and lasted for two weeks. Two reminders were sent. The second online survey focused on the management section of the guideline. The survey began on 14 October 2020 and also last for two weeks. Three reminders were sent.

Both surveys were conducted using LimeSurvey and were structured as follows: the participants were shown each of the draft recommendations. Changes to the wording of the recommendation compared to the previous version of the guideline from 2016 were marked clearly using a different colour. Each draft recommendation was presented alongside the following information: the justification for the recommendation (for consensus-based recommendations), and the evidence for the recommendation (for evidence-based recommendations). Changes in the justification and evidence texts compared to the previous version of the guideline from 2016 were also marked clearly using a different colour. Participants were given the option to agree with draft recommendation, to agree with the draft recommendation but to comment on it, or to disagree with the draft recommendation and to comment on it and provide an alternative draft recommendation.

All members of the expert panel were eligible for voting (irrespective of whether they declared to have personal-financial conflicts of interests. A total of 50 of the 61 members of the expert panel (81.9%) participated in the first survey, and 60 of the 61 members (98.4%) participated in the second survey[2]. Agreement rates were generally very high (above 90%), and several suggestions for editorial changes to the wording of recommendations were taken into account.

CONSENSUS CONFERENCE (3 DECEMBER 2020)

Consensus conference participants were a large international group of experts consisting of (a) the expert panel and (b) a much broader group of participants, who had registered for the conference out of interest in the subject and were qualified as physicians regularly involved in treating patients with urticaria or had been involved in basic or clinical research in the field. The aim of including this broader group was to help to ensure the regional implementability of the guideline, both by drawing upon the group's expertise and by asking them to serve as ambassadors for the guideline and its implementation.

[2] 3 new members joined at a later date

Before the consensus conference, we incorporated the results of the online pre-voting into the draft recommendations, and made the evidence-to-decision frameworks available for download to all participants registered to take part in the consensus conference on 3 December 2020. Those who wanted to vote during the conference also had to submit the conflict of interest declaration. Everyone except for those employed at a pharmaceutical company were eligible for voting and received a code to access the live polls.

Alexander Nast moderated the conference and used the nominal group technique to facilitate the consensus process. First, each draft recommendation and the justification or evidence was presented, discussed one by one, which was followed by final consensus voting. As this was a hybrid conference, we used the SLI.DO tool to create live voting polls. Those participants, who declared to work for industry, did not receive the access code.

In the guideline itself, the strength of the consensus reached for each recommendation is reported as shown in Table 7.

TABLE 7: STRENGTH OF CONSENSUS

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

Each recommendation in the guideline is formatted as shown in Box 3-Box 5. At the top of each box, the question of interest is given (e.g., "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 6. In Box 3, for example, we can see that a strong recommendation is being made (i.e., "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 4. In this case, the strength of consensus and the evidence base are given for each recommendation separately.

In Box 5, 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.

BOX 3: 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 4: 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 5: 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		

DEVELOPING TEXTS

Following the consensus conference, the guideline coordinators Prof. Marcus Maurer and Prof. Torsten Zuberbier amended the text from the 2017 guideline in line with points generated by the expert panel during the pre-conference online voting as well as the in line with points discussed during the consensus conference. The draft was reviewed by the group (see below).

INTERNAL AND EXTERNAL REVIEW

The draft guideline was sent to the expert group for internal review on 26 April 2021, and the group had two weeks, until 10 May 2021, to provide their written feedback on the document. All comments received were reviewed and implemented by the guideline co-coordinators (MM & TZ). The resulting document was subsequently sent the funding societies of EuroGuiDerm and all members of the EDF for external review from 21 June to 31 July 2021. Links to the draft document were also disseminated via various social media channels so that anyone coud provide their feedback. As with the internal review, all comments were reviewed and implemented by the guideline co-coordinators (MM & TZ).

DISSEMINATION AND IMPLEMENTATION

The dissemination and implementation activities pursued in related to the present guideline are given below in Table 8.

QUALITY STANDARDS AND MONITORING INDICATORS

It was agreed during the consensus conference that quality standard and monitoring indicators could be agreed at the local level in each of the participating countries, and that panel members would feed back any relevant information in this regard.

EVALUATION METHODS

Monitoring and evaluation of the implementation of the guideline will take place at the national level.

- Change in practice performance
- Change in health outcomes
- Change in end-user knowledge and understanding

RESOURCE IMPLICATIONS

Because this is an international guideline, the resource implications of the recommendations therein will vary from jurisdiction to jurisdiction. It was agreed during the consensus conference that panel members would feed back any relevant information on this point.

RESEARCH PRIORITIES

The expert group identified a range of need for further research. The list below is identical to the list given in Table 12 of the main guideline document[1]:

- 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 H1-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 H2-antihistamines, montelukast, sulfones (dapsone/sulfasalazine), methotrexate, azathioprine
- Development of better treatment options
- Trials and licensing of 2nd generation H1-antihistamines for the treatment of children below 6 months of age

STRENGTHS AND LIMITATIONS

This section is, in large part, identical to that in the previous Methods and Evidence Report[3]

The strength of the body of evidence presented lies within the application of rigorous and systematic methods as recommended by Cochrane and the GRADE working group, which we describe in detail here. We also used Evidence to Decisions Frameworks to include the balance of potentially desirable and undesirable effects as well as to raise awareness about the feasibility, costs, equity and acceptability of the intervention. These barriers to implementation need to be considered within the national or local context.

The evidence identified regarding the treatment of urticaria is very diverse and many studies report different outcomes at different time points. The reader should be aware of the issue of multiplicity, although we specified outcomes and time points a priori in the protocol. There were no protocol amendments or deviations from the protocol.

Concerning statistical limitations, for different comparisons we did pool two trials although the detection of heterogeneity using the I^2 statistics is suboptimal. It is also worth mentioning that the UAS7 is scored in two different ways. When pooling data, we did not differentiate between these two systems. However, Karsten Weller (expert, Weller et al [unpublished data]) found that these two scoring systems are very similar. With regard to the assessment of various outcomes, some trials did not report whether the outcome was patient or physician-assessed. Each unclear case was debated within the review team and a pragmatic approach was chosen when handling the data.

Due to resource restrictions we neither searched for further evidence by hand nor did we search grey literature repositories or trial registers. However, a large number of experts were involved in the guideline development process, and no missing or ongoing trials were evident. The review protocol specified that each primary study had to report the necessary data to be able to calculate effect

measures. Reporting was often suboptimal and studies had to be excluded. We did not qualitatively report on these studies, and this choice may have introduced reporting bias.

During the guideline development process, no patient representative or patient organization was involved, although we did attempt to invite patient representative from the European Federation of Allergy and Airways Diseases Patients' Associations (EFA).

UPDATE AND METHODS

The expert panel will decide if and when an update is necessary, at the latest five years from the date of publication of the 2020/21 guideline.

TABLE 8: DISSEMINATION PLAN

Audience	**Responsible Subcommittee member(s)**	**Communication and/or implementation tools to be used**	**Time at which they are to be developed, piloted or to take place**	**Is EuroGuiDerm support needed, and if yes what kind of support?**
Dermatologists, allergologists	Marcus Maurer, Torsten Zuberbier, Corinna Dressler	Full guideline & methods report & flow charts – EDF website	After completion of external review	Yes, CD /MD editorial support
Dermatologists , allergologists, researchers	Marcus Maurer, Torsten Zuberbier, Corinna Dressler	Journal publication	The draft version will be submitted to an academic journal at the same time as it is submitted for external review	Yes, CD /MD editorial support
Dermatologists , allergologists	Marcus Maurer, Torsten Zuberbier,	Implementation slides	At the same time as the guideline draft	–
Physicians, researchers, patients, public,	Corinna Dressler	TWITTER , EuroGuiDerm Newsletter	After completion of external review	Corinna Dressler

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APPENDIX 1: SEARCH STRATEGIES

Date: 15.05.2020

Database: Ovid MEDLINE(R) ALL 1946 to May 14, 2020

Hits: 238

1. exp Urticaria/

2. "urticaria*".ab,kf,ti.

3. hives.ab,kf,ti.

4. w?eals.ab,kf,ti.

5. "dermatographi*".ab,kf,ti.

6. ("factiti*" adj3 urticaria*).ab,kf,ti.

7. ((cold or heat or pressure or solar) adj3 urticaria*).ab,kf,ti.

8. (vibratory adj3 angio?edema).ab,kf,ti.

9. ((cholinergic or contact) adj3 urticaria*).ab,kf,ti.

10. ((aquagenic or (water adj3 induc*)) adj3 urticaria*).ab,kf,ti.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. randomized controlled trial.pt.

13. controlled clinical trial.pt.

14. randomized.ab.

15. placebo.ab.

16. clinical trials as topic.sh.

17. randomly.ab.

18. trial.ti.

19. or/12-18

20. exp animals/ not humans.sh.

21. 19 not 20

22. 11 and 21

23. ("201604*" or "201605*" or "201606*" or "201607*" or "201608*" or "201609*" or "201610*" or "201611*" or "201612*" or "2017*" or "2018*" or "2019*" or "2020*").dt.

24. 22 and 23

Date: 15.05.2020

Database: Embase Classic+Embase 1947 to 2020 May 14

Hits: 959

1. exp *Urticaria/

2. "urticaria*".ab,kw,ti.

3. hives.ab,kw,ti.

4. w?eals.ab,kw,ti.

5. "dermatographi*".ab,kw,ti.

6. ("factiti*" adj3 urticaria*).ab,kw,ti.

7. ((cold or heat or pressure or solar) adj3 urticaria*).ab,kw,ti.

8. (vibratory adj3 angio?edema).ab,kw,ti.

9. ((cholinergic or contact) adj3 urticaria*).ab,kw,ti.

10. ((aquagenic or (water adj3 induc*)) adj3 urticaria*).ab,kw,ti.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. Randomized controlled trial/

13. Controlled clinical study/

14. random$.ti,ab.

15. randomization/

16. intermethod comparison/

17. placebo.ti,ab.

18. (compare or compared or comparison).ti.

19. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

20. (open adj label).ti,ab.

21. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

22. double blind procedure/

23. parallel group$1.ti,ab.

24. (crossover or cross over).ti,ab.

25. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

26. (assigned or allocated).ti,ab.

27. (controlled adj7 (study or design or trial)).ti,ab.

28. (volunteer or volunteers).ti,ab.

29. human experiment/

30. trial.ti.

31. or/12-30

32. random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

33. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

34. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

35. (Systematic review not (trial or study)).ti.

36. (nonrandom$ not random$).ti,ab.

37. “Random field$”.ti,ab.

38. (random cluster adj3 sampl$).ti,ab.

39. (review.ab. and review.pt.) not trial.ti.

40. "we searched".ab. and (review.ti. or review.pt.)

41. "update review".ab.

42. (databases adj4 searched).ab.

43. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

44. Animal experiment/ not (human experiment/ or human/)

45. or/32-44

46. 31 not 45

47. 11 and 46

48. ("201604*" or "201605*" or "201606*" or "201607*" or "201608*" or "201609*" or "201610*" or "201611*" or "201612*" or "2017*" or "2018*" or "2019*" or "2020*").dc.

49. 47 and 48

Date: 13.05.2020

Database: Cochrane Central Register of Controlled Trials (CENTRAL)

Hits: 856

ID	Search
#1	urticaria*:ti,ab,kw (Word variations have been searched)
#2	MeSH descriptor: [Urticaria] explode all trees
#3	hives:ti,ab,kw (Word variations have been searched)
#4	wheals:ti,ab,kw (Word variations have been searched)
#5	weals:ti,ab,kw (Word variations have been searched)
#6	dermatographi*:ti,ab,kw (Word variations have been searched)
#7	factiti* near/3 urticaria*:ti,ab,kw (Word variations have been searched)
#8	(cold or heat or pressure or solar) near/3 urticaria*:ti,ab,kw (Word variations have been searched)
#9	vibratory near/3 angioedema:ti,ab,kw (Word variations have been searched)
#10	((cholinergic or contact) near/3 urticaria*):ti,ab,kw (Word variations have been searched)
#11	((aquagenic or (water near/3 induc*)) near/3 urticaria*):ti,ab,kw (Word variations have been searched)
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

Limit #12 to Publication Year from 2016 to 2020 and Cochrane Library publication date from Apr 2016 to May 2020

APPENDIX 2: LIST OF EXCLUDED FULL-TEXT PUBLICATIONS

Author	Title	Year	Reason for exclusion
	Corrigendum to: effect of omalizumab on angioedema in H1-antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial (Allergy, (2016), 71, (1135-1144), 10.1111/all.12870)	2017^	erratum not relevant
	3rd Inflammatory Skin Disease Summit-The Translational Revolition	2018^	Mitra already included
M. Abajian	Rupatadine 20 mg and 40 mg are Effective in Reducing the Symptoms of Chronic Cold Urticaria	2016^	included in 2016
Anonymous	Correction: (The Journal of Allergy and Clinical Immunology (2016) 137 (5)(1627) (S0091674915012476) (10.1016/j.jaci.2015.08.023))	2016^	no study reported
A. Avci	Does omalizumab treatment affect serum dehydroepiandrosterone sulphate levels in chronic idiopathic urticaria?	2019^	no relevant comparison group
J. Bernstein	Changes in symptom control, work productivity and activity impairment, and anxiety symptoms in chronic idiopathic urticaria patients after 24-week treatment with omalizumab	2017^	XTEND-CIU
T. Casale	Safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria (CIU/CSU): Pooled analysis of three randomized, double-blind, placebo-controlled Phase III studies (ASTERIA I, ASTERIA II, and GLACIAL)	2015^	individual studies included in 2016 (abstract with pooled safety data only here)
T. B. Casale	Exploring demographic and clinical differences among omalizumab responders and non-responders: interim results from a 48-week, phase IV study of omalizumab in chronic idiopathic/spontaneous urticaria	2017^	xtend study, no additional data
T. B. Casale	Impact of omalizumab on patient reported outcomes in chronic idiopathic urticaria: results From XTEND-CIU, A 48-Week, randomized, placebo-controlled study	2018^	no relevant outcome/comparison /study design
T. B. Casale	Study design, baseline and open-label results from XTEND-CIU: a phase IV, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of omalizumab through 48 weeks in patients with chronic idiopathic urticaria	2017^	xtend study, focus on open-label period
T. B. Casale	Omalizumab response in patients with chronic idiopathic urticaria: Insights from the XTEND-CIU study	2018^	no comparison w1-w12
G. Cervellin	Is adrenaline misused in anaphylaxis treatment? Experience of a large, urban emergency department: Review of 589 cases	2016^	retrospective study
H. C. Chang	Efficacy of autologous whole blood or serum therapy for chronic spontaneous urticaria: a systematic review and meta-analysis	2019^	systematic review
C. I. Chi	Efficacy and safety of Acrivastine combined with Clarityne in patients with chronic and intractable urticaria	2017^	trial register
H. Y. Chiu	An investigator-initiated, open-label, single-center, proof-of-concept-study of omalizumab in patients with poorly controlled acute urticaria	2017^	no comparison group
H. Cornillier	Chronic spontaneous urticaria in children - a systematic review on interventions and comorbidities	2018^	systematic review
Ctri	Usefulness and safety of conventional and modified self-serum therapy in long standing generalised itch and wheals of skin	2016^	trial register
Ctri	â??A clinical trial to study the beneficial effects of the drug â??â??Rupatadineâ?? in â??â??Allergic skin disease	2017^	trial register
Ctri	Effect of bepotastine besilate and levocetrizine in urticaria disease of skin	2017^	trial register

Ctri	Comparison of Methotrexate with Cetirizine versus increasing doses of cetirizine in patients with chronic urticaria	2017^	trial register
Ctri	Assessing and comparing efficacy of cyclosporine versus azathioprine in CRU	2017^	trial register
Ctri	A Comparative Clinical Study to Evaluate the effectiveness of DEXAMETHASONE-AGIO Injection in the treatment of severe or incapacitating allergic conditions of skin and respiratory tract	2017^	trial register
Ctri	Comparison of safety and usefulness of levocetrizine tablet and bepotastine tablet in patients suffering from hives for more than 6 weeks	2018^	trial register
Ctri	Comparision between Levocetrizine versus combination of Levocetrizine and Desloratidine in the management of urticaria	2018^	trial register
Ctri	A trial comparing psychological therapy with steroids in treatment of chronic urticaria patients	2019^	trial register
G. N. Dakhale	Comparison of efficacy, safety and cost-effectiveness of rupatadine and olopatadine in patients of chronic spontaneous urticaria: a randomized, double-blind, comparative, parallel group trial	2016^	no relevant comparison
C. Dressler	Chronic inducible urticaria: A systematic review of treatment options	2018^	systematic review
F. R. Euctr	COrticosteroids in acUte uRticAria in emerGency dEpartment	2018^	trial register
A. Y. Finlay	Omalizumab substantially improves dermatology-related quality of life in patients with chronic spontaneous urticaria	2017^	three phase III studies ASTERIA I, ASTERIA II and GLACIAL already included in 2016 (DLQI data reported here only)
A. Fukunaga	Efficacy of switching to bilastine, a histamine H1 receptor antagonist, in patients with chronic spontaneous urticaria (H1-SWITCH): study protocol for a randomized controlled trial	2020^	protocol
A. Gimenez-Arnau	Predicting return of chronic idiopathic urticaria symptoms following omalizumab treatment discontinuation: exploratory analysis of phase III data	2017^	pooled data
A. M. Gimenez-Arnau	Improvement of sleep in patients with chronic idiopathic/spontaneous urticaria treated with omalizumab: results of three randomized, double-blind, placebo-controlled studies	2016^	already included, ASTERIA I, ASTERIA II, and GLACIAL
K. Godse	Subcutaneous autologous serum therapy in chronic urticaria	2016^	study already included (Godse 2017)
K. Godse	Subcutaneous autologous serum therapy in chronic urticaria	2019^	study already included (Godse 2017)
K. V. Godse	Subcutaneous Autologous Serum Therapy in Chronic Spontaneous Urticaria	2017^	no relevant outcome data (was extracted but data not suitable for analysis)
T. Grieco	IFN-gamma/IL-6 and related cytokines in chronic spontaneous urticaria: evaluation of their pathogenetic role and changes during omalizumab therapy	2020^	no relevant control group
W. Gulliver	Omalizumab treatment response after dose step-up in patients with chronic diopathic/spontaneous urticaria (CIU/CSU): results from the OPTIMA study	2017^	optima study, no relevant comparison
M. Hide	Efficacy and safety of omalizumab for the treatment of refractory chronic spontaneous urticaria in Japanese patients: Subgroup analysis of the phase 3 POLARIS study	2018^	subgroup analysis of POLARIS (Hide 2017)
M. Hide	Efficacy and safety of omalizumab in Japanese and Korean patients with chronic spontaneous/idiopathic urticaria (CSU/-CIU): results from the phase III POLARIS study	2017^	POLARIS abstract, no additional data (Hide 2018)
M. Hide	Efficacy and safety of omalizumab in Japanese and Korean patients with chronic idiopathic/ spontaneous urticaria (CIU/CSU): results from the Phase III POLARIS study	2018^	POLARIS abstract, no additional data (Hide 2018)

M. Hide	Long-term safety and efficacy of rupatadine in Japanese patients with itching due to chronic spontaneous urticaria, dermatitis, or pruritus: A 12-month, multicenter, open-label clinical trial	2019^	no comparison group
M. Hide	Efficacy of increased dose of rupatadine up to 20 mg on itching in Japanese patients due to chronic spontaneous urticaria, dermatitis, or pruritus: A post hoc analysis of phase III clinical trial	2019^	original article does not include a comparison group (Hide 2019 https://doi.org/10.1016/j.jdermsci.2019.05.008)
M. Hide	Efficacy and safety of bilastine in Japanese patients with chronic spontaneous urticaria: a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II/III study	2016^	same DOI as Hide 2017
Irct20171030037093N	The effect of Atorvastatin and Cetirizine on the improvement of clinical symptoms of patients with chronic urticaria	2019^	trial register
Irct20171222037986N	Serum Autologous Therapy in Idiopathic Chronic Urticaria	2019^	trial register
A. Johnston	Influence of prolonged treatment with omalizumab on the development of solid epithelial cancer in patients with atopic asthma and chronic idiopathic urticaria: A systematic review and meta-analysis	2019^	systematic review
U. Jprn	Effect of anti-immunoglobulin E therapy on chronic prurigo and cholinergic urticaria	2017^	trial register
A. Kaplan	Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria	2016^	included in 2016 (Astreia I+II, GLacial)
A. P. Kaplan	Diagnosis, pathogenesis, and treatment of chronic spontaneous urticaria	2018^	review
D. Kiruba and S. Srinivasan	Evaluate the efficacy of autologous serum therapy (AST) in patients with chronic idiopathic urticaria	2019^	no available in the interlibray loan system
E. Kocaturk	Management of chronic inducible urticaria according to the guidelines: a prospective controlled study	2017^	no comparison group
P. Kolkhir	New treatments for chronic urticaria	2020^	review
G. N. Konstantinou	Omalizumab administration for refractory to H1- chronic urticaria prevents respiratory illnesses	2017^	no relevant study design
G. N. Konstantinou and D. Karapiperis	Omalizumab administration in nonatopic chronic spontaneous urticaria patients prevents respiratory illnesses	2017^	no relevant study design
P. Korczynska-Krawczyk	The effect of levocetirizine and montelukast on clinical symptoms, serum level and skin expression of COX-1 and COX-2 enzymes in patients suffering from chronic autoimmune urticaria - a pilot study	2020^	no relevant comparison, chronic autoimmune urticaria (subgroup of spontanious urticaria)
K. Kulthanan	Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review	2018^	systematic review
K. Kulthanan	Factors Predicting the Response to Cyclosporin Treatment in Patients With Chronic Spontaneous Urticaria: A Systematic Review	2019^	systematic review
K. Kulthanan	Delayed Pressure Urticaria: A Systematic Review of Treatment Options	2020^	systematic review
D. E. S. Larenas-Linnemann	Update on Omalizumab for Urticaria: What's New in the Literature from Mechanisms to Clinic	2018^	review
S. Leducq	Efficacy and safety of methotrexate add-on therapy versus placebo for patients with chronic spontaneous urticaria resistant to H1-antihistamines: a randomized, controlled trial	2019^	already included (Laducq 2020)
S. E. Liang	Use of Dapsone in the Treatment of Chronic Idiopathic and Autoimmune Urticaria	2019^	no relevant study design

M. Lopez and L. Navajas-Galimany	What are the effects of omalizumab in refractory chronic spontaneous urticaria?	2015^	systematic review
A. Maouia	CRP relevance in clinical assessment of chronic spontaneous urticaria Tunisian patients	2017^	no relevant outcome
R. Maoz-Segal	Treatment with combination of omalizumab and immuno-suppressor and high dose anti-histamine for resistant severe chronic spontaneous urticaria (Late Breaking Abstract)	2019^	no relevant study design
N. Marrouche and H. C. Williams	Letter in response to "Effectiveness and safety of levocetirizine 10 mg versus a combination of levocetirizine 5 mg and montelukast 10 mg in chronic urticaria resistant to levocetirizine 5 mg: A double-blind, randomized, controlled trial" by Sarkar et al	2018^	no trial
M. Maurer	Characterization of responders to omalizumab: exploratory analysis of phase III data from patients with chronic spontaneous urticaria	2016^	no relevant outcome
M. Maurer	Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence	2018^	systematic review
M. Maurer	Omalizumab is effective and well tolerated in cold urticaria: results of CUTEX, a multicentre randomized placebo-controlled trial	2016^	study already included (Metz 2017 CUTEX https://doi.org/10.1016/j.jaci.2017.01.043) no additional data
M. Maurer	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	2017^	already included, DLQI, pooled analyses of ASTERIA I, ASTERIA II and GLACIAL
M. Metz	Omalizumab is effective and safe in symptomatic dermographism: results of UFO, a multicentre randomized, placebocontrolled trial	2016^	abstract included in 2016, data from fulltext DOI: 10.1016/j.jaci.2017.01.042 (Mauer 2017) added; CINDU
M. Metz	Omalizumab normalizes the gene expression signature of lesional skin in patients with chronic spontaneous urticaria: a randomized, double-blind, placebo-controlled study	2019^	NCT01599637, main study (Metz 2017) already included
M. Metz	Omalizumab normalizes gene expression in lesional skin of patients with chronic spontaneous urticaria: Results from a randomized, double-blind, placebo-controlled study	2016^	study already included Metz 2017/2019 NCT01599637
M. Metz	Omalizumab normalizes gene expression in lesional skin of patients with chronic idiopathic/spontaneous urticaria: results from a randomized, double-blind, placebo-controlled study	2016^	study already included Metz 2017/19 NCT01599637 DOI: 10.1111/all.13547
B. Mitra	A randomized, double-blind, placebo-controlled study of monoclonal Anti-IgE antibody Omalizumab in the management of pruritus in chronic spontaneous urticaria in the pediatric population	2018^	abstract only, no numerical data reported (omalizumab in children)
B. Mitra	Randomized, double-blind, placebocontrolled study of monoclonal anti-IgE antibody omalizumab in the management of pruritus in chronic spontaneous urticaria in the pediatric population	2017^	abstract only, no numerical data reported (omalizumab in children)
Nct	Treatment of Idiopathic Angioedema With Xolair as Add-on Therapy	2016^	trial register
Nct	To Assess and Compare the Efficacy of Cyclosporine Versus Azathioprine in the Treatment of Chronic Refractory Urticaria	2017^	trial register
Nct	Adding a Short Burst of Corticosteroid to the Conventional Treatment of H1 Antihistamines in Emergency Department	2017^	trial register
Nct	Efficacy of Antihistamine Dosing-up and add-on Treatment With H2-receptor Antagonist	2017^	trial register
Nct	Study of Efficacy and Safety of Xolair® (Omalizumab) in Chinese Patients With Chronic Spontaneous Urticaria	2017^	trial register

Z. Novak	Safety and tolerability of bilastine 10 mg administered for 12 weeks in children with allergic diseases	2016^	no separate result for urticaria population
K. Oomen-Welke and R. Huber	Intramuscular autologous blood therapy - a systematic review of controlled trials	2019^	systematic review
P. Palungwachira	A randomized controlled trial of adding intravenous corticosteroids to H1 antihistamines in patients with acute urticaria	2020^	no relevant population (acute urticaria)
Y. S. Pathania	Comparing azathioprine with cyclosporine in the treatment of antihistamine refractory chronic spontaneous urticaria: A randomized prospective active-controlled non-inferiority study	2019^	no relevant comparison (azathioprine vs CSA)
P. Potter	Rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2-11 years	2016^	study already included in 2016
K. Rabeti Moghadam	Efficacy of autologous serum therapy in patients with chronic idiopathic urticaria compared to control group assessed by dermatological life quality index(DLQI) questionnaire (Late Breaking Abstract)	2018^	no relevant time point (DLQI after 16w)
M. Rodriguez	Pharmacokinetics and safety of bilastine in children aged 6 to 11 years with allergic rhinoconjunctivitis or chronic urticaria	2020^	main text Vosmediano 2019
N. P. M. Rubini	Effectiveness and safety of Omalizumab in the treatment of chronic spontaneous urticaria: Systematic review and meta-analysis	2019^	systematic review
S. S. Saini	Erratum: Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria who Remain Symptomatic on H<inf>1</inf> Antihistamines: A Randomized, Placebo-Controlled Study (Journal of Investigative Dermatology (2015) 135(1) (67-75) (S0022202X15370652) (10.1038/jid.2014.306))	2015^	no additional data
M. Scarupa	Characteristics of CIU responders/nonresponders after 24 weeks of omalizumab treatment: Results from X-tend-CIU	2017^	X-tend-CIU
M. Singh and S. Kaur	Relative Efficacy of Seven Common H1 Receptor Antagonist Antihistamines in Chronic Idiopathic Urticaria	1987^	not available in the German interlibrary loan system
D. Skoner	Clinical characteristics of adolescent and adult patients with refractory chronic idiopathic urticaria (CIU) in three phase III studies with omalizumab	2018^	baseline data for omalizumab studies separated by age (but pooled)
H. Sofen	Changes in dermatology quality of life, sleep, and symptoms during the 24-week open-label period of XTEND-CIU: a phase IV, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of omalizumab through 48 weeks	2017^	no comparison w1-w12
P. Staubach	Omalizumab effectively reduces angioedema episodes in patients with chronic idiopathic/spontaneous urticaria (CIU/CSU)	2016^	xact study included in 2016
P. Staubach	Less angioedema, more quality of life and lower signs of depression in CSU during omalizumab treatment	2016^	xact study included in 2016
P. Staubach	Effect of omalizumab on angioedema in H1 -antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial	2016^	publication included in 2016
Z. Sthoeger	Omalizumab in patients with severe active chronic spontaneous urticaria (CSU) heavily treated with corticosteroids and cyclosporine	2017^	restrospective study, looking for full study report, maybe https://www.sciencedirect.com/science/article/pii/S2213219817307195?via%3Dihub#!
D. Stull	Correlation between changes in urticaria symptoms and sleep experience in patients with chronic spontaneous/idiopathic urticaria (CSU/CIU): Results from two randomized, doubleblind, placebo-controlled Phase III trials of omalizumab	2015^	study already included (ASTERIA I and GLACIAL)

G. Sussman	Safety and tolerability of omalizumab in patients with chronic idiopathic/spontaneous urticaria: results from the OPTIMA study	2018^	optima study,
G. Sussman	Design and rationale of OPTIMA, a study to evaluate retreatment, extension, or step-up therapy with omalizumab in patients with chronic idiopathic/spontaneous urticaria (CIU/CSU)	2017^	optima study, no relevant comparison
G. Sussman	Omalizumab retreatment of patients with chronic idiopathic/spontaneous urticaria (CIU/CSU) after initial response and relapse: primary results of the OPTIMA Study	2017^	withdrawl phase not controlled (PBO)
G. Sussman	Omalizumab Re-Treatment and Step-Up in Patients with Chronic Spontaneous Urticaria: OPTIMA Trial	2020^	withdrawl phase not controlled (PBO)
G. Sussman	Omalizumab treatment, re-treatment and step-up treatment associated with reduced angioedema rates: results from the optima study	2019^	withdrawl phase not controlled (PBO)
G. Sussman	Omalizumab retreatment of patients with chronic idiopathic urticaria / chronic spontaneous urticaria following return of symptoms: primary results of the optima study	2017^	withdrawl phase not controlled (PBO) OPTIMA
G. Sussman	Design and rationale of the optima study: retreatment or step-up therapy with omalizumab in patients with chronic idiopathic/ spontaneous urticaria (CIU/CSU)	2017^	optima study, no relevant comparison
G. Sussman	Patient demographics and real-world use of omalizumab for the treatment of chronic spontaneous/idiopathic urticaria in Canada: Analysis of patient support program data	2016^	no relevant study design
G. Sussman	Ligelizumab is well tolerated and exhibits a safety profile similar to omalizumab and placebo in patients with chronic spontaneous urticaria	2019^	only adverse events (%) reported
Tctr	A randomized, double-blinded, controlled trial of adding a short burst of corticosteroid to the conventional treatment of H1 antihistamines	2018^	trial register
M. D. Tharp	Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients with Chronic Idiopathic (Spontaneous) Urticaria: A Meta-analysis of "real-world" Evidence	2019^	systematic review
M. D. Tharp	Effectiveness of omalizumab in adolescent and adult patients with chronic idiopathic/spontaneous urticaria: Meta-Analysis of "real-world" evidence	2018^	systematic review
H. Tran Thi	The efficacy of a two-fold increase of H1-antihistamine in the treatment of chronic urticaria - The Vietnamese experience	2019^	no relevant comparison (updosing in two diff. H1AH 2nd gen)
V. Vozmediano	Model-informed pediatric development applied to bilastine: Analysis of the clinical PK data and confirmation of the dose selected for the target population	2019^	no relevant study design
J. Wang	Effects of Desloratadine Citrate Disodium on Serum Immune Function Indices, Inflammatory Factors and Chemokines in Patients with Chronic Urticaria	2019^	no relevant comparison (H1AH 2nd gen vs H1AH 2nd gen, 1-fold each)
B. Wedi	Mast cell-mediated angioedema - Current and future therapies. [German]	2019^	no primary study
K. Weller	Omalizumab improves angioedema-related quality of life impairment in chronic spontaneous urticaria patients: results from the X-ACT study	2018^	x-act study already included in 2018 (Staubach 2016; abstact here only reported AE qol)
K. Weller	Efficacy of bilastine updosing in refractory moderate to severe chronic spontaneous urticaria	2016^	no comparison group (at the same time); see Weller 2018 https://doi.org/10.1111/all.13494
K. Weller	Omalizumab improves angioedemarelated quality of life impairment in chronic spontaneous urticaria patients: results from the X-ACT study	2017^	x-act study already included in 2018 (Staubach 2016; abstact here only reported AE qol)
A. Yagami	One-year safety and efficacy study of bilastine treatment in Japanese patients with chronic spontaneous urticaria or pruritus associated with skin diseases	2016^	same DOI as Yagami 2017

A. Yagami	One-year safety and efficacy study of bilastine treatment in Japanese patients with chronic spontaneous urticaria or pruritus associated with skin diseases	2017^	no comparison group
J. L. Zazzali	Angioedema in the omalizumab chronic idiopathic/spontaneous urticaria pivotal studies	2016^	no relevant outcome (angiodema)
Z. T. Zhao	Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials	2016^	systematic review
D. Zheng and X. Yang	Clinical observation on the therapeutic effect of desloratadine citrate disodium in the treatment of chronic urticaria and changes in IL4, IL18, IL23 and IL-33 levels before and after treatment	2017^	2nd gen vs another 2nd gen H1AH (both 1-fold)

ABBREVIATIONS

AEs	Adverse events
AH	Antihistamines
BID	Twice a day
CI	Confidence interval
CIndU	Chronic inducible urticaria
CU/CSU	Chronic urticaria, chronic spontaneous urticaria
GRADE	Grading of Recommendations Assessment, Development and Evaluation
EtD	Evidence-to-Decision frameworks
ITT	Intention-to-treat
MD	Mean difference
PICO	Patient - Intervention - Comparison - Outcome
PP	Per-protocol
QD	Once a day
QW	Once a week
RCT	Randomized controlled trials
RR	Risk ratio
SD	Standard deviation
SoF	Summary of findings