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POSITION PAPER

Methods report on the development of the 2013 revision and update of the EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria

T. Zuberbier[1], W. Aberer[2], R. Asero[3], C. Bindslev-Jensen[4], Z. Brzoza[5], G. W. Canonica[6], M. K. Church[1], L. F. Ensina[7], A. Giménez-Arnau[8], K. Godse[9], M. Gonçalo[10], C. Grattan[11], J. Hebert[12], M. Hide[13], A. Kaplan[14], A. Kapp[15], A. H. Abdul Latiff[16], P. Mathelier-Fusade[17], M. Metz[1], S. S. Saini[18], M. Sánchez-Borges[19], P. Schmid-Grendelmeier[20], F. E. R. Simons[21,22], P. Staubach[23], G. Sussman[24], E. Toubi[25], G. A. Vena[26], B. Wedi[15], X. J. Zhu[27], A. Nast[1,†] & M. Maurer[1,†]

[1]Department of Dermatology and Allergy, Allergy-Centre-Charité, Charité – University Hospital Berlin, Berlin, Germany; [2]Department of Dermatology, Medical University of Graz, Graz, Austria; [3]Allergy Clinic, Clinica San Carlo, Paderno Dugnano, Italy; [4]Department of Dermatology and Allergy Centre, Odense University Hospital and University of Southern Denmark, Odense, Denmark; [5]Department of Internal Diseases, Allergology and Clinical Immunology in Katowice, Medical University of Silesia, Katowice, Poland; [6]Respiratory Diseases & Allergy, University of Genoa, IRCCS AOU SanMartino, Genoa, Italy; [7]Federal University of Sao Paulo, Sao Paulo, Brazil; [8]Hospital del Mar. Parc de Salut Mar, Universitat Autònoma, Barcelona, Spain; [9]Department of Dermatology, Dr. D. Y. Patil Medical College & Hospital, Nerul, Navi Mumbai, India; [10]Clinic of Dermatology, Faculty of Medicine and University Hospital, Coimbra, Portugal; [11]St John's' Institute of Dermatology, Guy's' and St Thomas' Hospitals NHS Foundation Trust, London, UK; [12]Center for Applied Research on Allergy Québec, Québec, QC, Canada; [13]Department of Dermatology, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; [14]Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA; [15]Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany; [16]Department of Paediatrics, Pantai Hospital Kuala Lumpur, Bangsar, Malaysia; [17]Department of Dermatology and Allergy, University Hospital of Tenon, Paris, France; [18]Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA; [19]Allergy and Clinical Immunology Department, Centro Médico-Docente La Trinidad, Caracas, Venezuela; [20]Allergy Unit, Department of Dermatology, University Hospital, Zürich, Switzerland; [21]Department of Pediatrics & Child Health, University of Manitoba; [22]Department of Immunology, University of Manitoba, Winnipeg, MB, Canada; [23]Department of Dermatology, University Medical Center Mainz, Mainz, Germany; [24]Division of Allergy and Clinical Immunology, University of Toronto, Toronto, ON, Canada; [25]Bnai-Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel; [26]Unit of Dermatology and Venereology, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy; [27]Department of Dermatology, Peking University First Hospital, Beijing, China

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Correspondence
Torsten Zuberbier, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany.
Tel.: +49-30-450-518135
Fax: +49-30-450-518919
E-mail: torsten.zuberbier@charite.de

†These authors contributed equally to this work.
*See section on 'External review'.

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Abstract

This methods report describes the process of guideline development in detail. It is the result of a systematic literature review using the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) methodology and a structured consensus conference held on 28 and 29 November 2012, in Berlin. It is a joint initiative of the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) with the participation of delegates of 21 national and international societies. This guideline covers the definition and classification of urticaria, taking into account the recent progress in identifying its causes, eliciting factors and pathomechanisms. In addition, it outlines evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria. This guideline was acknowledged and accepted by the European Union of Medical Specialists (UEMS) and is published in *Allergy* 2014; **69**:868–887.

This methods report provides information on the development process of the 2013 revision and update of the European Academy of Allergology and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA^{2}LEN), European Dermatology Forum (EDF), and World Allergy Organization (WAO) guideline for the definition, classification, diagnosis, and management of urticaria. It is an update of the previous international guidelines on urticaria (1, 2).

The guideline update was developed in alignment with the quality criteria contained within the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, and the German Association of Scientific Medical Societies (AWMF).

The update of the urticaria guidelines was made using a structured development process comprising a systematic search of the literature in the relevant databases, a systematic evaluation of the search results, and a consensus conference based on formal consensus methodology (structured consensus conference).

Methods

Nomination of experts

In January 2012, GA^{2}LEN started the updating process for the urticaria guidelines by contacting international and national societies for allergy and dermatology to explore whether they wanted to participate in the guideline revision and update process. The societies that committed to participate are listed in Table 1. Already the last version of this guideline was based on the involvement of GA^{2}LEN, EAACI, and EDF in cooperation with European Academy of Dermatology and Venereology (EADV) and the WAO.

All participating societies were asked to name their delegates to the expert panel and authorship groups, taking into account that:

1 delegates were allowed to represent more than one society and
2 panel members and co-authors of the previous guideline were recommended to the societies as possible delegates.

As for the previous revision and update of urticaria guidelines, the consensus conference including the discussion and voting procedure was open to all experts interested in participating. Hence, the 2013 update and revision of the guideline is based on the contributions of the society-nominated expert panel members as well as on other experts interested. This 'enlarged consensus group' is believed to broaden the acceptance of the guidelines and helping their dissemination and implementation.

In addition, the consensus conference was attended by two chronic urticaria (CU) patients with good knowledge of the English language treated at the urticaria clinic of the Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, as well as a delegate of the nonprofit patient interest organization UNEV (currently the only patient interest organization in the field of urticaria in Europe).

For a detailed overview of participants of the consensus conference, see Table 2.

Selection of relevant key questions to be addressed during the update and revision process of the guideline

Prior to the consensus meeting, a list of questions was developed by the expert panel's steering committee (Zuberbier, Maurer, Nast; Berlin) based on the previous guidelines. This list of questions was circulated among all panel members for review. They were then rated with respect to their importance, and a final selection was prepared by the steering committee and agreed upon by the expert panel.

Check for existing guidelines and systematic reviews

The update and revision of the guidelines was based on three previous versions of the guidelines, which resulted from urticaria guideline consensus conferences in 2000, 2004, and 2008 (1–6). Other guidelines were not systematically assessed. Reasons were limited resources and the fact that the previous versions were the most suitable basis for the development of the 2013 guideline.

Literature search and update based on existing systematic reviews

The formalized literature research performed entailed:

1 the previous versions of the guidelines (1–6). For the previous versions of the guideline, a systematic search as described in the respective publications had been conducted and all randomized trials published up to and in 2008 had been evaluated and documented in GRADE tables.
2 a new literature search for all publications as of 2008.

To find relevant trials, we performed systematic searches of the databases MEDLINE and EMBASE (for search strategies, see Table 3) and hand-searches of abstracts at

Abbreviations

AAAAI, American Academy of Allergy, Asthma & Immunology*; AEDV, Spanish Academy of Dermatology and Venereology; ASBAI, Brazilian Association of Allergy and Immunopathology; CDA, Chinese Dermatologist Association; CSACI, Canadian Society of Allergy and Clinical Immunology; DDG, German Society of Dermatology; DGAKI, German Society of Allergology and Clinical Immunology; EAACI, European Academy of Allergology and Clinical Immunology; EDF, European Dermatology Forum; ESCD, European Society of Contact Dermatitis; GA^{2}LEN, 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; MSAI, Malaysian Society of Allergy and Immunology; ÖGDV, Austrian Society for Dermatology; SDF, French Society of Dermatology; SGDV, Swiss Society for Dermatology and Venereology; SPDV, Portuguese Society of Dermatology and Venereology; UNEV, Urticaria Network; WAO, World Allergy Organization.

Table 1 Societies that participated in the 2013 update and revision of the urticaria guidelines

Societies involved in the Urticaria Guidelines 2013						
ÖGDV, Austrian Society for Dermatology	EAACI, European Academy of Allergology and Clinical Immunology	WAO, World Allergy Organization	ASBAI, Brazilian Association of Allergy and Immunopathology	GA^{2}LEN, Global Allergy and Asthma European Network	AAAAI, American Academy of Allergy, Asthma & Immunology*	IADVL, Indian Association of Dermatologists, Venereologists and Leprologists
CSACI, Canadian Society of Allergy and Clinical Immunology	JDA, Japanese Dermatological Association	DDG, German Society of Dermatology	MSAI, Malaysian Society of Allergy and Immunology	SDF, French Society of Dermatology	SGDV, Swiss Society for Dermatology and Venereology	IAACI, Israel Association of Allergy and Clinical Immunology
EDF, European Dermatology Forum	DGAKI, German Society of Allergology and Clinical Immunology	CDA, Chinese Dermatologist Association	UNEV, Urticaria Network	SPDV, Portuguese Society of Dermatology and Venereology	ESCD European Society of Contact Dermatitis	AEDV, Spanish Academy of Dermatology and Venereology

*See section on 'External review'.

international allergy congresses between 2008 and 2012. Search date was February 22, 2012, assessed via OVID.

The results were then screened, evaluated, and included or excluded by two (in some cases three) assessors (Maurer, Metz, and/or Zuberbier). The bibliographic information was then transferred to an EndNote database, and the full texts were obtained if available.

Standardized inclusion/exclusion and data extraction

Identified literature was evaluated by two of the assessors (Maurer and Zuberbier). The data generated were compared with each other; any discrepancies were reviewed by a third assessor (Metz) and finally resolved through discussion.

Literature had to fulfill specific criteria in order to be included into the guideline:

1 direct relevance to the specific issue.
2 no serious methodological limitations in the study with respect to the quality of the information for the selected outcome as determined by the assessors.

The included literature was selected with respect to their hierarchy in the 'evidence pyramid', for example if a good systematic review was available and up to date no further systematic analysis of randomized controlled trials (RCTs) or cohort studies was carried out. This was chosen in case of existing high-quality RCTs; no further systematic analysis of cases series or case reports was carried out.

Use of the GRADE system and grading of evidence

In the previous version of the guideline, studies were evaluated using the GRADE approach. The key principle of this approach is to provide transparency as well as clear and explicit criteria for assessing the quality of evidence and for grading the strength of recommendations (7) based on risk *vs* benefits. The strength of a recommendation and the quality of supporting evidence were assessed independently for each recommendation, taking into consideration negative and positive effects such as side-effects, reduction of urticaria symptoms, practicability, feasibility, and costs.

Importantly, the GRADE system permits strong recommendations supported by low- or, very rarely, very low-quality evidence from downgraded RCTs or observational studies. On the other hand, weak recommendations may be based on high-quality evidence if other factors are important, for example the price of a treatment option.

The phrase 'we recommend' was used for strong recommendations and 'we suggest' for weak recommendations in order to adhere to the same methodology used for the Allergic Rhinitis and its Impact on Asthma Guideline 2008 update (8).

Consensus conference

The structured consensus conference 'URTICARIA 2012' took place in Berlin, Germany, on November 28/29, 2012. The conference was supervised by PD Dr Alexander Nast, who is a certified guideline advisor and moderator of the AWMF. During the conference, updates on the scientific

Table 2 The experts nominated by the commissioning societies formed the steering committee

	Name	City/country	Institution/company	Delegate of
1	Aberer, Werner	Graz (Austria)	Department of Dermatology, Medical University of Graz, Graz, Austria	ÖGDV
2	Asero, Riccardo	Milano (Italy)	Allergy Clinic, Clinica San Carlo, Paderno Dugnano (MI), Italy	EAACI
3	Bindslev-Jensen, Carsten	Odense (Denmark)	Department of Dermatology and Allergy Centre, Odense University Hospital and University of Southern Denmark, Odense, Denmark	GA^{2}LEN
4	Brzoza, Zenon	Katowice (Poland)	Department of Internal Diseases, Allergology and Clinical Immunology in Katowice, Medical University of Silesia, Poland	EAACI
5	Canonica, Walter G.	Genova (Italy)	Respiratory Diseases & Allergy, University of Genoa, IRCCS AOU SanMartino, Genoa, Italy	WAO
6	Church, Martin	Berlin (Germany/UK)	Department of Dermatology and Allergy, Allergy-Centre-Charité, Charité – University Hospital Berlin, Berlin, Germany	GA^{2}LEN
7	Cox, Linda	Davie (FL, USA)	Nova Southeastern University School of Osteopathic Medicine, Davie	AAAAI*
8	Ensina, Luis Felipe	São Paulo (Brasil)	Federal University of Sao Paulo, Sao Paulo, Brazil	ASBAI
9	Giménez-Arnau, Ana	Barcelona (Spain)	Hospital del Mar. Parc de Salut Mar, Universitat Autònoma Barcelona, Spain	EAACI and AEDV
10	Godse, Kiran	Mumbai (India)	Department of Dermatology, Dr. D. Y. Patil Medical College & Hospital, Nerul, Navi Mumbai, India	IADVL
11	Gonçalo, Margarida	Coimbra (Portugal)	Clinic of Dermatology, Faculty of Medicine and University Hospital, Coimbra, Portugal	SPDV and ESCD
12	Grattan, Clive	Norfolk (UK)	St John's' Institute of Dermatology, Guy's' and St Thomas' Hospitals NHS Foundation Trust, UK	EAACI
13	Hébert, Jaques	Québec (Canada)	Center for Applied Research on Allergy Québec, Québec, Canada	CSACI
14	Hide, Michihiro	Hiroshima (Japan)	Department of Dermatology, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan	JDA
15	Kaplan, Allen	Charleston (SC, USA)	Department of Medicine, Division of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology, Medical University of South Carolina, Charleston, SC, USA	WAO
16	Kapp, Alexander	Hannover (Germany)	Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany	DDG
17	Lang, David	Cleveland (OH, USA)	Respiratory Institute, Cleveland Clinic	AAAAI*
18	Latiff, Abdul A.H.	Kuala Lumpur (Malaysia)	Department of Paediatrics, Pantai Hospital Kuala Lumpur, Bangsar, Kuala Lumpur, Malaysia	MSAI
19	Mathelier-Fusade, Pascale	Paris (France)	Department of Dermatology and Allergy, University Hospital of Tenon, Paris, France	SDF
20	Maurer, Marcus	Berlin (Germany)	Department of Dermatology and Allergy, Allergy-Centre-Charité, Charité – University Hospital Berlin, Berlin, Germany	EAACI
21	Metz, Martin	Berlin (Germany)	Department of Dermatology and Allergy, Allergy-Centre- Charité, Cahrité – University Hospital Berlin, Berlin, Germany	EAACI
22	Nast, Alexander	Berlin (Germany)	Department of Dermatology and Allergy, Allergy-Centre-Charité, Charité – University Hospital Berlin, Berlin, Germany	Moderator
23	Saini, Sarbjit	Baltimore (USA)	Johns Hopkins Asthma and Allergy Center, Baltimore (MD), USA	AAAAI and WAO
24	Sánchez-Borges, Mario	Caracas (Venezuela)	Allergy and Clinical Immunology Department Centro Médico-Docente La Trinidad, Caracas, Venezuela	WAO

Table 2 (Continued)

	Name	City/country	Institution/company	Delegate of
25	Schmid-Grendelmeier, Peter	Zürich (Switzerland)	Allergy Unit, Department of Dermatology, University Hospital, Zürich, Switzerland	SGDV
26	Simons, Estelle	Manitoba (Canada)	Department of Pediatrics & Child Health, Department of Immunology, University of Manitoba, Canada	CSACI
27	Staubach, Petra	Mainz (Germany)	Department of Dermatology, University Medical Center Mainz, Germany	UNEV
28	Sussman, Gordon	Toronto (Canada)	Division of Allergy and Clinical Immunology, University of Toronto, Toronto (ON), Canada	CSACI
29	Toubi, Elias	Haifa (Israel)	Bnai-Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel	IAACI
30	Vena, Gino	Bari (Italy)	Unit of Dermatology and Venereology, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy	EDF
31	Wedi, Bettina	Hannover (Germany)	Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany	DGAKI
32	Zhu, Xuejun	Beijing (China)	Department of Dermatology, Peking University First Hospital, Beijing, China	CDA
33	Zuberbier, Torsten	Berlin (Germany)	Department of Dermatology and Allergy, Allergy-Centre-Charité, Charité – University Hospital Berlin, Berlin, Germany	EDF and GA^{2}LEN

*See section on 'External review'.

knowledge in the field of urticaria were presented in short, focused presentations by panel members. This was followed by two interactive sessions, one dedicated to the nomenclature, classification, and diagnostic algorithm in urticaria and the other to its treatment. During these sessions, the recommendations prepared by the panel members were presented to the participants and voted on.

Voting was done with the use of red and green voting cards and performed in a structured way. Only 'yes' or 'no' voting was allowed in order to ensure clear majority decisions. If a recommendation did not achieve 90% agreement during the first voting, the respective recommendation was re-discussed and, if needed, rephrased. In order to pass in the second voting round, a minimum of >75% agreement had to be achieved.

Under headline 3.2, all the preselected questions were addressed and under 3.4 the corresponding recommendations are listed as well as the protocol of the different alternatives, which were discussed and voted on during the consensus meeting.

External review

The guidelines underwent an extensive external review. From March 26, 2013, until April 26, 2013, the guideline was reviewed and finally endorsed by the participating societies.

During this review process, societies were granted to make amendments only limited to scientific errors. This regulation was a consequence of the voting rules agreed upon for the process developing the guideline.

Specifically, the wording of the recommendations had to remain unchanged during the review process. The recommendations are ultimately a result of several perspectives, involving the votes of the panel members delegated by the societies, as well as additional opinions

Table 3 Search strategies

Suche vom 22.02.2012
1. exp Angioedema/
2. "angioedema*".ti.
3. "angiooedema*".ti.
4. "quincke* edema*".ti.
5. "quincke* oedema*".ti.
6. "angioneuro* edema*".ti.
7. "angioneuro* oedema*".ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Urticaria/
10. "urticaria*".ti.
11. "hives*".ti.
12. 9 or 10 or 11
13. 8 or 12
14. limit 13 to (yr="2009 -Current" and (english or german))

Urtikaria_Medline in Process

Suche vom 22.02.2012
1. "angioedema*".ti.
2. "angiooedema*".ti.
3. "quincke* edema*".ti.
4. "quincke* oedema*".ti.
5. "angioneuro* edema*".ti.
6. "angioneuro* oedema*".ti.
7. 1 or 2 or 3 or 4 or 5 or 6
8. "urticaria*".ti.
9. "hives*".ti.
10. 8 or 9
11. 7 or 10
12. limit 11 to (yr="2009 -Current" and (english or german))

Urtikaria_Embase

Suche vom 22.02.2012
1. *angioneurotic edema/
2. "angioedema*".ti.

Table 3 (Continued)

3. "angiooedema*".ti.
4. "quincke* edema*".ti.
5. "quincke* oedema*".ti.
6. "angioneuro* edema*".ti.
7. "angioneuro* oedema*".ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. *urticaria/
10. "urticaria*".ti.
11. "hives*".ti.
12. 9 or 10 or 11
13. 8 or 12
14. limit 13 to ((english or german) and yr="2009 -Current")
Urtikaria_Cochrane
Suche vom 22.02.2012
1. exp Angioedema/
2. "angioedema*".ti.
3. "angiooedema*".ti.
4. "quincke* edema*".ti.
5. "quincke* oedema*".ti.
6. "angioneuro* edema*".ti.
7. "angioneuro* oedema*".ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Urticaria/
10. "urticaria*".ti.
11. "hives*".ti.
12. 9 or 10 or 11
13. 8 or 12
14. limit 13 to (yr="2009 -Current" and (english or german))

that were taken into consideration during the consensus meeting: practicing physicians in urticaria as well as affected patients.

However, all societies involved had the possibility to not endorse the guideline upon review or to provide additional comments regarding aspects and conditions specific to their countries or geographic region.

The AAAAI made the decision not to endorse the guideline as they felt there were too many differences to an US Urticaria Practice Parameter under development. The AAAAI therefore decided to define their contribution to the guideline as 'with participation of the American Academy', but not as an endorsing founder society.

Other participants

The consensus conference 'URTICARIA 2012' including the discussion and voting process was open to all experts interested in participating. Hence, the 2013 guidelines resulted from discussions and a consensus by delegates nominated by scientific societies as well as other experts (Table 4).

Selection of relevant interventions and key questions

The following questions were suggested and considered relevant to be answered by the guideline. Depending on

Table 4 Additional members of the consensus group

Last name	First name	Country code
Abajian	Marina	DE
Al Ahmad	Mona	KW
Altrichter	Sabine	DE
Ardelean	Elena	DE
Asoyan	Armenak	RU
Balaña Vilanova	Montserrat	ES
Balp	Maria-Magdalena	CH
Barry	Kay	UK
Bech-Thomsen	Niels	DK
Ben Hamida	Amna	LB
Bkov	Per Stahl	DK
Boccon-Gibod	Isabelle	FR
Bonnekoh	Hanna	DE
Boonpiyathad	Sawad	TH
Bräutigam	Matthias	DE
Broom	Brian	NZ
Bruggink	T.I.M.	NL
Brzostek	Dorota	PL
Bubolic	Suzy	CA
Bukovskis	Maris	LV
Burum-Auensen	Espen	NO
Campos	Regis	BR
Casanovas	Mireia	ES
Cassano	Nicoletta	IT
Chapman-Rothe	Nadine	DE
Chen	Hong	CN
Chen	Yue	CN
Chiriac	Anca	RO
Chiriac	Anca	RO
Chomiciene	Anzelika	LT
Cruz	Ana Teresa	PT
Curto	Laia	ES
Czarnecka-Operacz	Magdalena	PL
Dahlborn	Anna-Karin	SE
Danilycheva	Inna	RU
Daschner	Alvaro	ES
Dibra	Marinela	AL
Dickson	Marion	UK
Dieng	Mame Thierno	SN
Dieng	Souleymane	CI
Douladiris	Nikolaos	GR
Drobik	Olga	RU
El Amine	Milad	CI
Enevoldsen	Henriette Køhler	DK
Falkencrone	Sidsel	DK
Fang	Hong	CN
Ferrer Puga	Marta	ES
Fields	Stephen	CA
Figliomeni	Maria	US
FitzGibbon	Joe	IE
Fitzharris	Penny	NZ
Fomina	Daria	RU
Ford	Julie	CH
Frambach	Yvonne	DE
Frølund	Lars	DK

Table 4 (Continued)

Last name	First name	Country code
Fucci	Virginia	IT
Gallo	Rosella	IT
Gao	Guangcheng	CN
Garcia	Roberto	US
Georgiou	Panayiotis	UK
Gericke	Janine	DE
Gigauri	Tinatin	GE
Goryachkina	Lyudmila	RU
Goujon	Catherine	FR
Greaves	Malcolm	UK
Groffik	Adriane	DE
Hao	Fei	CN
Hawro	Tomasz	DE
Heiberg	Jens	DK
Hermes	Barbara	DE
Herwig	Edda	DE
Hoting	Edo	DE
Houston	Parul	CH
Huller	Elke	DE
Ilharco	Ana	PT
Isidoro Garcia	Olga	ES
Izquierdo	Iñaki	ES
Jakob	Thilo	DE
Jentzsch	Claudia	DE
Johannsen	Henning	AU
Jun Young	Lee	KR
Karaulov	Alexander	RU
Kiechle	Tamara	CH
Kinaciyan	Tamar	AT
Knol	Edward	NL
Kober	Anita	SE
Korczynska	Paulina	PL
Koroleva	Maria	RU
Koti	Ioanna	DE
Kowalski	Marek	PL
Kraas	Luise	DE
Krajny	Milos	CA
Krause	Karoline	DE
Kressel	Gaby	DE
Kruszewski	Jerzy	PL
Kuhn	Christof	CH
Kurzawa	Ryszard	PL
Landro	Linn	NO
Lange	Dirk	DE
Lawlor	Frances	UK
Lecocq	Brigitte	FR
Leru	Polliana	RO
Leslie	Tabi	UK
Li	Chengxin	CN
Li	Linfeng	CN
Lippert	Undine	DE
Liveris	Andreas	CY
Magerl	Markus	DE
Maggi	Enrico	IT
Mahler	Vera	DE
Makris	Michael	GR
Marrouche	Nadine	UK
Marsland	Alexander	UK
Martine	Lefebvre	BE
Martinez-Escala	M.-Estela	ES
Mathelier-Fusade	Pascale	FR
Maurer	Marcus	DE
Merk	Hans	DE
Metz	Martin	DE
Millington	George	UK
Młynek	Agnieszka	DE
Mobacken	Håkan	SE
Möckel	Andy	DE
Mokronosova	Marina	RU
Nakonechna	Alla	UK
Nast	Alexander	DE
Nosbaum	Audrey	FR
Ohanyan	Tatevik	DE
Pawliczak	Rafał	PL
Pelck	Inger	DK
Pereira	Catarina	PT
Pigatto	Paolo Daniele Maria	IT
Popescu	Florin Dan	RO
Preisz	Paul	AU
Redlin	Andreas	DE
Reiter	Nadine	DE
Ress	Krista	EE
Roduit	Caroline	CH
Rogala	Barbara	PL
Röhrbein	Jan	DE
Romano	Antonino Gaetano	IT
Rosen	Karin	US
Rupnik	Helena	SI
Saini	Sarbjit	US
Sánchez-Borges	Mario	VE
Santamaria Masdeu	Eva	ES
Santa-Marta	Cristina	PT
Saraiva	Tania	PT
Scarupa	Mark	US
Scerri	Lawrence	MT
Schmid-Grendelmeier	Peter	CH
Schoepke	Nicole	DE
Schwab	Katharina	DE
Sie	C.L.	NL
Siebenhaar	Frank	DE
Silva	Barbara	BR
Silvestre Salvador	Juan Francisco	ES
Slaby	Katarzyna	PL
Smeets	Serge	NL
Spiewak	Radoslaw	PL
Spohr	Adrian	DE
Stasii	Ecaterina	MD
Stockman	Annelies	BE
Szepietowski	Jacek	PL
Tarrago Tillo	Javier	ES

Table 4 (Continued)

Last name	First name	Country code
Tedeschi	Donatella	IT
Tempels-Pavlica	Zana	NL
Thielen	Antje	DE
Treudler	Regina	DE
Tsakona	Chrys	UK
Tumelero	Melissa	BR
van Dalen	G.	NL
Vardanyan	Karina	RU
Veleiro Perez	Beatriz	ES
Vella Briffa	Domenic	MT
Vestergaard	Christian	DK
Wagner	Nicola	DE
Weber-Arden	Julia	DE
Weller	Karsten	DE
Wieczorek	Dorothea	DE
Yong	Adrian	UK
Zazzali	James	US
Zhang	Jianzhong	CN
Zuotao	Zhao	CN

feasibility, they were answered on an evidence-based or on a consensus-based/good clinical practice level. For every sentence, it is clearly stated whether the recommendation is given based on 'clinical practice' or whether a 'level of evidence' is provided.

1 Should the current classification be maintained in urticaria?
2 Should the current activity score (UAS7) be maintained assessing severity in urticaria?
3 Should routine diagnostic measures be performed in acute urticaria?
4 Should routine diagnostic measures be performed in chronic spontaneous urticaria (CSU)?
5 Should extended diagnostic measures be performed in CSU?
6 Should routine diagnostic measures be performed in inducible, nonspontaneous subtypes of urticaria?
7 Which instrument should be used to measure quality of life (QoL) in urticaria?
8 Should patients with an allergic sensitization (positive specific IgE/skin prick test) avoid certain food items?
9 Should treatment aim at complete symptom control in urticaria?
10 Are modern second-generation H1-antihistamines (AHs) to be preferred over first-generation H1-AHs in the treatment of urticaria?
11 Are modern second-generation AHs as first-line treatment in urticaria to be preferred against other licensed medication?
12 Is an increase in the dose to fourfold of modern second-generation H1-AHs useful as second-line treatment and to be preferred over other treatments in urticaria?
13 Are H2-AHs useful in the treatment of urticaria as third-line therapy?
14 Is cyclosporin A useful as add-on treatment in patients unresponsive to high doses of H1-AHs as third-line treatment?
15 Is omalizumab (OMA) useful in the treatment of patients unresponsive to high doses of H1-AHs as third-line treatment?
16 Should oral corticosteroids be used in the treatment of urticaria?
17 Should leukotriene antagonists be used in the third-line treatment of urticaria?
18 Is dapsone useful in the treatment of urticaria as third-line therapy?
19 Should the same treatment algorithm be used in children?
20 Should the same treatment algorithm be used in pregnant women and during lactation?
21 Are pseudoallergen-free diets useful in the extended diagnostic program of CSU?
22 Should modern second-generation AHs be taken regularly or as needed?
23 Should different H1-AHs be used at the same time?
24 If there is no improvement, should higher than fourfold doses of H1-AHs be used?

Systematic literature search

The systematic search identified 2804 hits in all databases, and after checking for doubles, 1956 hits remained for abstract screening (see Table 5).

After abstract screening, 188 full texts were obtained, and from these, 67 were included into the body of evidence for the new guidelines.

Consensus conference and voting results

Should the current classification be maintained in urticaria?
We recommend the use of this version of the classification of the 2013 guideline revision (strong recommendation/clinical consensus, accepted with 100%).

Reasoning/summary from discussion. The current classification was proposed for the first time in the 2008 revision and update of the urticaria guideline (1) and has been adopted by

Table 5 Hits in systematic literature search

	All	Doubles excluded
MEDLINE	815	793
MEDLINE in Process	170	168
EMBASE	1771	978
Cochrane Library	48	17
Total	2804	1956

multiple national or regional guidelines. Furthermore, the classification has been adhered to in all trials published since then and in the vast majority of publications. In addition, the current classification, which explicitly omits the term 'chronic idiopathic urticaria', has been used in regulatory documents. Based on this, we recommend the continued use of this updated version of the classification. Inducible urticaria subtypes are chronic diseases as well but as in many other allergic diseases, symptoms depend on the presence of the trigger.

See Supporting Evidence in Table 6.

Should the current UAS7 be maintained assessing severity in urticaria?

We recommend the use of UAS7 to assess severity (strong recommendation/clinical consensus, accepted with 100%).

Reasoning/summary from discussion. The UAS7 is a validated tool for assessing disease activity in CSU and was already recommended to be used in routine clinical practice and clinical trials in the previous guideline. Recently another score, the Urticaria Severity Score (USS), has been developed and validated (9). The USS combines assessment of signs and symptoms with QoL questions. The UAS7, however, remains the recommended gold standard for assessing activity (strong recommendation/high-quality evidence). It should be used as originally established, without modification (i.e., once daily per patient recording of wheal numbers (no wheals: score value = 0, 1–20 wheals: score value = 1, 21–50 wheals: score value = 2, >50 wheals: score value = 3, no pruritus: score value = 0, mild pruritus: score value = 1, moderate pruritus: score value = 2, strong pruritus: score value = 3)). The use of the original UAS7 ensures the comparability of previous and new trials, because the UAS7 has been used in the majority of trials published during the last 5 years. To ensure the future comparability of new trials, we recommend adherence to the currently proposed UAS7 (strong recommendation/high-quality evidence) in clinical trials. This decision is not based on inferiority of the USS to the UAS7 score as head-to-head investigations are missing. Reasons are practical considerations: UAS7 is now established and changing it would not allow comparison of future trials with older ones. Both scores may be employed by physicians in daily practice.

See Supporting Evidence in Table 7.

Should routine diagnostic measures be performed in acute urticaria?

We recommend against routine diagnostic measures in acute urticaria (strong recommendation/clinical consensus, accepted with 100%).

Reasoning/summary from discussion. Acute urticaria in more than 95% of the cases is self-limited and it usually has a duration of <2 weeks. In addition, acute urticaria can generally be treated satisfactorily with AHs and it is frequently associated with upper respiratory tract viral infections where no clinical consequence would follow from determining the specific virus. Based on these facts, the previous version of the guideline recommended that no routine diagnostic measures be performed in acute urticaria except in the case of a clear suspicion from the patient history of an eliciting agent. Since the last guideline, no systematic reviews or trials have been published showing a reasonable cost/benefit ratio of routine diagnostics in acute urticaria. We recommend not using routine diagnostic measures in acute urticaria except in the case of a suspicion clearly derived from the patient history for an eliciting agent. This decision is based mainly on a negative cost/benefit ratio.

See Supporting Evidence in Table 8.

Table 6

Investigated study	Study design	*P*-value outcome	Limitations	Inconsistency, indirectness, imprecision	Quality	Importance	Year	Citation
	S3 level guideline	n.a.	None		High	High	2009	Zuberbier et al. (2)

n.a., not applicable.

Table 7

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Jariwala, Moday (9)	Prospective	n.a.	Validated in 80 patients, single center only	High	High	2009
Mlynek, Zalewska-Janowska (10)	Prospective	$P = 0.05$ correlated later with QoL	Validated in three patients, single center	High	High	2008

n.a., not applicable; QoL, quality of life.

Table 8

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Zuberbier, Ifflander (11)	Prospective, open, monocentric, observational studying course of untreated firstly diagnosed acute urticaria under 2 forms of standard treatment	n.a	Old study which was never repeated, high rate of spontaneous remission reflects clinical experience of all consensus participants	Low	High	1996

n.a., not applicable.

Should routine diagnostic measures be performed in CSU?
We recommend for only very limited routine diagnostic measures in CSU (strong recommendation/clinical consensus, accepted with 100%).

Reasoning/summary from discussion. In the previous version of the guidelines, the recommendation to limit routine diagnostic measures in CSU was based on the notion that the diagnostic workup in CSU patients should be a two-step approach: Step one is aimed at the exclusion of severe underlying diseases and avoidance of NSAIDs (routine/basic diagnostic measure to be performed in all patients) and Step two is the identification of underlying causes (extended diagnostic measures as indicated by patient history; to be performed in patients with longstanding and/or severe disease). In the previous guidelines, this conclusion was based on the fact that no new literature had been published contradicting this approach.

See Supporting Evidence in Table 9.

Should extended diagnostic measures be performed in CSU?
We recommend for only limited extended diagnostic measures in CSU based on patient history (strong recommendation/clinical consensus, accepted with 100%).

Reasoning/summary from discussion. The previous version of the guideline recommends the use of extended diagnostic measures in CSU patients who exhibit a severe and/or longstanding disease and who provide clues for underlying cause(s) from their history. The current revision and update of the guideline maintains this recommendation. Disease activity and duration should be assessed. If the search for underlying causes is warranted, patients should be investigated for clues by taking a detailed history. For example, gastric pain may point to Helicobacter pylori infection, coexisting autoimmune disorders may suggest autoreactive mechanisms, reports of exacerbation of symptoms following the consumption of certain foods may indicate pseudoallergy as the cause. Several studies have shown the use of extended diagnostic measures to be helpful in the identification of underlying causes and in improving patient management if based on the patient's history.

See Supporting Evidence in Table 10.

Should routine diagnostic measures be performed in inducible, nonspontaneous subtypes of urticaria?
We recommend limiting routine diagnostic measures to determining the threshold of eliciting factors in inducible urticaria subtypes (strong recommendation/clinical consensus, accepted with 100%).

Table 9

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Smith (12)	Systematic review of 29 studies	n.a.	None	High	High	2011
Tarbox, Gutta (13)	Retrospective analysis of a random sample of adult patients with urticaria and/or angioedema from 2001 to 2009, 356 cases in total	n.a.	Diagnosis in patients was not standardized but based on individual decisions of differently treating physicians	Low	High	2011

n.a., not applicable.

Table 10

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Smith (12)	Systematic review	n.a.	Divergent studies included. In summary, additional tests are valuable only when based on history of patients	High	High	2011

n.a., not applicable.

Reasoning/summary from discussion. According to the existing version of the guidelines, routine diagnostic measures in inducible, nonspontaneous subtypes of urticaria should be limited to determining the nature of the inducing trigger and its threshold. This recommendation is based on the fact that the triggers, but not the underlying factors, are not known to cause the majority of inducible urticaria subtypes, so attempts to identify them are generally futile. Routine and specific diagnostic measures are thus only warranted in cases where CSU coexists in the same patient or in rare subtypes of urticaria, for example cold urticaria where underlying causes have been identified in few cases. Since the last guideline was published, no new evidence has been published.

See Supporting Evidence in Table 11.

Which instrument should be used to measure QoL in urticaria?
We recommend using the validated Chronic Urticaria QoL.

Questionnaire (CU-Q2oL) and The Angioedema Quality of Life Questionnaires (AE-QoL) instruments for assessing QoL impairment and to monitor disease activity (strong recommendation/clinical consensus, accepted with 100%).

Reasoning/summary from discussion. Previous studies have shown that the generic QoL instruments in medicine and even dermatology are not disease specific enough to really measure the impact of urticaria (both wheals and angioedema). Disease-specific instruments have been developed, and they have been recommended in the last guideline since they were validated. Therefore, we recommend using the validated CU-Q2oL and AE-QoL instruments for assessing QoL impairment and to monitor disease activity.

See Supporting Evidence in Table 12.

Should patients with an allergic sensitization (positive specific IgE/skin prick test) avoid certain food items?
We recommend that patients with a known allergic sensitization based on specific IgE to food should only avoid these food items if there is relevant information, for example double-blind (DB) oral provocation test or a clear history, to prove that the sensitization has a clinical relevance for urticaria (strong recommendation/high level of evidence, accepted with 100%).

Reasoning/summary from discussion. In the previous guidelines, it was recommended that patients with a known allergic sensitization based on specific IgE to food should only avoid these items, if there is relevant information (e.g., DB oral provocation test or a clear history) to prove that the sensitization has a clinical relevance for urticaria. In addition, however, it needs to be noted that food-allergic reactions, for example gastrointestinal problems, can occur independently of the urticaria. The recommendation is in line with the general principle of allergy that allergens should be avoided in those cases where clinically relevant symptoms are proven. In line with other guidelines in allergy, sensitization alone is no reason to avoid an allergen (strong recommendation/high level of evidence).

See Supporting Evidence in Table 13.

Table 11

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Zuberbier et al. (1)	S3 level guideline	n.a.	Based on few studies with low-level evidence having investigated the causative factors of inducible urticaria subtypes	High	High	2009

n.a., not applicable.

Table 12

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Baiardini et al. (14)	Consensus recommendations	n.a.	No original data presented	High	High	2011
Brzoza et al. (15)	Polish validation study, prospective, SKINDEX and DLQI controlled, $n = 126$	n.a.	Was not used to assess treatment responses	High		2011
Kocaturk et al. (16)	n.a. prospective					2012
Maurer et al. (17)	n.a. prospective, multicenter, RPC		Was not designed or powered to validate CU-Q2oL as a tool for measuring treatment responses	High		2011
Mlynek et al. (18)	n.a. prospective					2009
Weller et al. (19)	n.a. prospective					2012
Krause et al. (20)	n.a. prospective					2012

RPC, randomized *placebo* controlled; n.a., not applicable.

Table 13

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Zuberbier et al. (2)	S3 level guideline	n.a.	None	High	High	2009
Brozek, Bousquet (8)	WHO guideline	n.a.	None, based on GRADE	High	High	2010
Boyce et al. (21)	US guideline	n.a.	None, based on GRADE	High	High	2011

n.a., not applicable.

Should treatment aim at complete symptom control in urticaria?

We recommend aiming for complete symptom control in urticaria as safely as possible [strong recommendation/clinical consensus following the WHO constitution in conformity with the Charter of the United Nations (UN)] (accepted with 97%).

Reasoning/summary from discussion. The previous guidelines recommended aiming for complete symptom control in urticaria. A number of studies have shown that using the algorithm proposed, it is in many patients possible to achieve complete symptom control. Our recommendation is based on the principles of medicine laid down in the WHO constitution in conformity with the Charter of the UN: Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity. The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition (22). It is thus required to offer the patient as much benefit as possible. The recommendation can thus be maintained.

See Supporting Evidence in Table 14.

Are modern second-generation H1-AHs to be preferred over first-generation H1-AHs in the treatment of urticaria?

We recommend that modern second-generation H1-AHs are to be preferred over first-generation H1-AHs in the treatment of urticaria (strong recommendation/high level of evidence, accepted with 95%).

Discussed alternatives:

1 We recommend the use of modern second-generation H1-AHs over first-generation H1-AHs in the treatment of urticaria (strong recommendation/high level of evidence, voting result 97%).

Reasoning/summary from discussion. We recommend second-generation over first-generation oral H1-AHs (strong recommendation/high-quality evidence). In line with the ARIA guideline for patients with allergic rhinitis (Brozek et al. 20), this recommendation places a relatively high value on the reduction of adverse effects and a relatively low value on comparative efficacy of second-generation *vs* first-generation oral H1-AHs. Already the previous guidelines have recommended to prefer modern second-generation AHs over first-generation H1-AHs in the treatment of urticaria. Since publishing the previous guideline, no new studies with head-to-head trials showing a possible improved efficacy of first-generation H1-AHs have been published but new reviews on the risks of first-generation H1-AHs are available. Based on the benefit/risk ratio, first-generation H1-AHs carry a high underestimated risk potential also when given in the evening (changes in REM pattern, hangover of impaired cognitive functions the next day) and thus should be avoided in the treatment of urticaria.

See Supporting Evidence in Table 15.

Are modern second-generation AHs as first-line treatment in urticaria to be preferred over other licensed medication?

We recommend that modern second-generation H1-AHs are to be used as first-line treatment of urticaria (strong recommendation/high level of evidence, accepted with 100%).

Reasoning/summary from discussion. Modern second-generation H1-AHs have been recommended as first-line treatment in urticaria in the previous guideline. In fact, AHs are the only licensed treatment in urticaria except for corticosteroids

Table 14

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Zuberbier et al. (2)	S3 level guideline	n.a.	None	High	High	2009

n.a., not applicable.

Table 15

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year
Zuberbier et al. (2)	S3 level guideline	n.a.	Based on few studies with low-level evidence	High	High	2009
Church, Maurer (23)	Systematic review	n.a.	None	High	High	2010

n.a., not applicable.

in acute urticaria. Using modern second-generation H1-AHs as treatment in all subtypes of urticaria has been shown to be efficacious in many trials for all licensed modern second-generation H1-AHs. Modern second-generation H1-AHs have furthermore proven to be of excellent safety and are available at low cost. The recommendation of the previous guideline to use modern second-generation H1-AHs that do not cause sedation can therefore be maintained (strong recommendation/high-quality evidence). This recommendation does not exclude the option that in acute urticaria, or acute exacerbations of CU, corticosteroids may and should be applied simultaneously if symptom severity does not allow a stepwise administration.

See Supporting Evidence in Table 16.

Is an increase in the dose to fourfold of modern second-generation H1-AHs useful as second-line treatment and to be preferred over other treatments in urticaria?

We recommend a trial of up to fourfold dose of modern second-generation H1-AHs as second line in the algorithm of treatment (strong recommendation/high level of evidence, accepted with 98%).

Reasoning/summary from discussion. This treatment has meanwhile shown to be efficacious both in CSU and in inducible forms of urticaria. However, it must be noted that an increase in doses is not in the license of any of the modern second-generation H1-AHs (except 1- to 5-fold in fexofenadine and twofold in ebastine). It is, however, in the license of some old-generation sedating AHs, for example up to 10-fold for hydroxyzine. Other alternative medications investigated so far in urticaria are also not licensed and the licensed AHs all have a safety dossier on doses of at least up to fourfold, but dose-dependent side-effects vary between different modern second-generation AHs. Looking at the risk/benefit ratio with good high-quality level of evidence regarding the safety of updosing and sufficient evidence of the efficacy of updosing, the recommendation can be made to consider updosing up to fourfold as second level in the algorithm in the treatment of urticaria (strong recommendation/high-quality evidence for safety/high-quality evidence for efficacy in CU and cold urticaria; low-quality evidence for other subtypes of urticaria and no evidence in acute urticaria except widespread clinical use as direct trials are missing but a high-level circumstantial evidence based on the mode of action that updosing is useful also in other subtypes of urticaria). This recommendation also puts an emphasis on low costs compared to treatment with cyclosporin or OMA which are also part of the algorithm in level 3.

See Supporting Evidence in Table 17.

Are H2-AHs useful in the treatment of urticaria as third-line therapy?

We suggest the use of H2-AHs as add-on therapy to modern second-generation H1-AHs as a possible alternative treatment but not as first, second, or third line in the algorithm of treatment of urticaria (low recommendation/low level of evidence, voting result, accepted with 88%).

Discussed alternatives:

1 We recommend a trial of H2-AHs as add-on therapy to modern second-generation H1-AHs as third line in the algorithm of treatment of urticaria (strong recommendation/low level of evidence) (voting result, $< 50\%$).
2 We suggest a trial of H2-AHs as add-on therapy to modern second-generation H1-AHs but not as third line in the algorithm of treatment of urticaria (low recommendation/low level of evidence, voting result, $< 50\%$).
3 We do not recommend a trial of H2-AHs as add-on therapy to modern second-generation H1-AHs in the algorithm of treatment of urticaria (strong recommendation/low level of evidence, voting result, $< 50\%$).
4 We do not recommend a trial of H2-AHs as add-on therapy to modern second-generation H1-AHs (strong recommendation/low level of evidence, voting result, $< 50\%$).
5 We do not recommend the use of H2-AHs as add-on therapy to modern second-generation H1-AHs (strong recommendation/low level of evidence, voting result, $< 50\%$).

Reasoning/summary from discussion. A recent Cochrane analysis found that evidence does not support the previous recommendation to use H2-AHs because evidence of efficacy is lacking in view of the fact that no new studies have been performed. H2-AHs are thus not recommended in the algorithm of treatment (strong recommendation/high-quality evidence) but could in individual cases be considered as alternative treatment in level 3 as the costs are very low and they are available worldwide (weak recommendation/low-quality evidence).

See Supporting Evidence in Table 18.

Is cyclosporin A useful as add-on treatment in patients unresponsive to high doses of H1-AHs as third-line treatment?

We recommend a trial of cyclosporin A as add-on therapy to modern second-generation H1-AHs as third line in the algorithm of treatment of urticaria (strong recommendation/high level of evidence, voting result, accepted with 100%).

Reasoning/summary from discussion. In the previous guidelines, cyclosporin A as add-on treatment to fourfold doses of new-generation oral H1-AHs has been recommended as fourth line of treatment in the algorithm. This recommendation was already based on high-quality *placebo*-controlled double-blind randomized trials showing efficacy and safety. Since then, new trials have confirmed these data. We recommend using cyclosporin A as an add-on treatment in patients unresponsive to high doses of H1-AHs as third-line treatment in the appropriate clinical context, that is, no past history of malignancy, HIV, or other contraindications.

See Supporting Evidence in Table 19.

Is OMA useful in the treatment of patients unresponsive to high doses of H1-AHs as third-line treatment?

We recommend a trial of OMA as add-on therapy to modern second-generation H1-AHs as third line in the algorithm of

Table 16

Drug	Daily dose	Duration	N active drug/*placebo*	Study design	$P < 0.05$ *vs* PL	$P < 0.05$ *vs* compared drug	Remarks	Limitations	Quality	Importance	Year	Citation
Azelastine *vs* cetirizine	4, 10 mg	2 weeks	73/Az, 23/Cet (Plc 28)	DB PC COMP	Yes	No	Pruritus: Az > Cet; whealing: Cet > Az	Patients with urticaria were studied together with patients with other allergic diseases, for example allergic rhinitis			1998	Henz et al. (24)
Azelastine *vs* ebastine	4, 10 mg	3 weeks	Az 17, Eb 17, Plc 18	DB PC MC COMP	Yes	No		0	High	High	2001	Camarasa et al. (25)
Bilastine *vs* levocetirizine	20, 5 mg	4 weeks	173 (Bila) 165 (Levo) Plc 184	DB PC COMP	Yes	No		0	High	High	2010	Zuberbier, Oanta (26)
Cetirizine *vs* cetirizine	10 or 20 mg	15 days	30 Cet	DB CRO	Yes	–	Patients with angioedema were excluded	0	High	High	1988	Juhlin and Arendt (27)
Cetirizine *vs* astemizole	10 mg 10 mg	4 weeks	62 Cet, 62 Astem, 63 Plc	DB COMP	–	Yes	Wheal AS; Cet > Ast (.04)	0	High	High	1990	Alomar et al. (28)
Cetirizine	10 mg		28	DB PC CRO	Yes	–		0	High	High	1991	Goh et al. (29)
Cet, Astem	10 mg	4 weeks	62 Cet, 62 Astem (63 Plc)	DB PC CRO	Yes	n.s.		0	High	High	1991	Juhlin (30)
Cetirizine *vs* terfenadine	10 mg, 2 × 60 mg	20 days	15 Cet, 15 Terf	DB COMP	–	Yes	Cet > Terf	0	High	Low	1993	Andri et al. (31)
Cetirizine *vs* oxatomide	5 mg Cet, 25 mg Oxa	4 weeks	28 Cet, 29 Oxa	DB MC COMP (children 2–6 years)	–	No	Children with angioedema were excluded	0	High	High	2001	La Rosa et al. (32)
Cetirizine *vs* fexofenadine	10 mg Cet, 120 Fex	4 weeks	52 Cet, 45 Fex	DB COMP	–	Yes					2004	Handa et al. (33)
Desloratadine	5 mg	6 weeks	Des 95 (Plc 95)	DB PC MC	Yes	–		0	High	High	2001	Ring et al. (34)
Ebastine	10 mg	2 weeks	Eb 100 (Plc 104)	DB PC MC	Yes	–		0	High	High	1991	Peyri and Marron (35)
Ebastine *vs* terfenadine	10 mg Eb, 120 mg Terf	12 weeks	69 Eb, 69 Plc, 69 Terf	DB PC MC COMP	Yes	No		0	High	High	1996	Kalis (36)
Fexofenadine	20, 60, 120, or 240 mg	4 weeks	Fex 20 mg: 90, 60 mg: 90,	DB PC MC	Yes	–	Fex 60 = 120 = 240 > 20 mg – Fex				2000	Nelson et al. (37)

Table 16 (Continued)

Drug	Daily dose	Duration	N active drug/*placebo*	Study design	$P < 0.05$ *vs* PL	$P < 0.05$ *vs* compared drug	Remarks	Limitations	Quality	Importance	Year	Citation
			120 mg: 77, 240 mg 82 – all 2 × daily, Plc: 79				improved performance/ work productivity – BID trend to 240 superior 120					
Fexofenadine	2 × 60 mg	4 weeks	169 Fex, 158 Plc	DB PC MC	Yes	–		Sum of two identical studies	High	High	2000	Thompson et al. (38)
Fexofenadine	2 × 10 mg (78) or 2 × 60 mg (75) or 2 × 120 mg (73)	1 week	226–2 × 10 mg (78), 2 × 60 mg (75), 2 × 120 mg (73)	DB dose finding	–	Yes (compared to Fex 2 × 10 mg)	Fex 2 × 60 ($n = 75$) and 2 × 120 ($n = 76$) >2 × 10 mg ($n = 75$), efficiency proven in Japanese patients similar to American patients	0	High	High	2001	Kawashima and Harada (39)
Fexofenadine	180 mg	3 weeks	21 Fex, 21 Plc	DB PC	Yes	–		Low number	High	High	2002	Degonda et al. (40)
Mizolastine	10 mg	4 weeks	28 Miz, 28 Plc	DB PC MC	Yes	–		Low number, two centers only	High	High	1996	Brostoff et al. (41)
Mizolastine, loratadine	10 mg Miz, 10 mg Lora	4 weeks	88 Miz, 79 Lor, 80 Plc	DB PC MC COMP	Yes	No	No difference with respect to angioedema	0	High	High	1999	Dubertret et al. (42)
Mizolastine	10 mg	4 weeks	39 Miz, 39 Plc	DB PC MC	Yes	–		Not a primary report – cannot be	Low	Low	1999	Ring et al. (43)

Table 16 (Continued)

Drug	Daily dose	Duration	N active drug/*placebo*	Study design	$P < 0.05$ *vs* PL	$P < 0.05$ *vs* compared drug	Remarks	Limitations	Quality	Importance	Year	Citation
								included in this evaluation				
Mizolastine *vs* loratadine	10 mg Miz, 10 mg Lor	4 weeks	26 Miz, 35 Lor	DB COMP	–	No	Miz had a tendency to better reduce angioedema and the mean total duration of episodes	0	High	High	2000	Leynadier et al. (44)
Rupatadine	10 or 20 mg	4 weeks	10 mg–112; 20 mg–109 (113)	DB PC MC	Yes			0	High	High	2007	Gimenez-Arnau et al. (45)
Rupatadine	5, 10 or 20 mg	4 weeks	5 mg–68; 10 mg–73; 20 mg–67 (69)	DB PC	Yes		Trend analysis showed a dose-dependent improvement	0	High	High	2007	Dubertret et al. (46)
Levocetirizine	5 mg	4 weeks	81 (85)	DB PC MC	Yes			0	High	High	2006	Kapp and Pichler (47)

Az, azelastine; Cet, cetirizine; Plc, *placebo*; Eb, ebastine; Bila, bilastine; Levo, levocetirizine; DB, double blind; PC, *placebo* controlled; COMP, comparison; CRO, cross-over; MC, multicenter; Astem, astemizole; Terf, terfenadine; Oxa, oxatomide; Des, desloratadine; Miz, mizolastine; Lor, loratadine.

Table 17

Drug	Daily dose	Duration	N active drug/ *placebo*	Study design	$P < 0.05$ *P vs* PL	$P < 0.05$ *P vs* compared drug	Remarks	Limitations	Quality	Importance	Year	Citation
Cetirizine	10 *vs* 30 mg	2–1 week 10 mg, 1 week 30 mg	22	Open-label CSU	n.a.	n.s.	(i) Open label; (ii) only increased to threefold not fourfold as in guideline	See remarks. ASST more frequently positive (72%) than in average CU population (approx. 30%)	Low	High	2007	Asero (48)
Rupatadine	10 *vs* 20 mg	4 weeks	112 Rup 10 mg, 109 Rup 20 mg, 113 Plc	DB, PC, MC	Yes	0.01			High	High	2007	Gimenez-Arnau et al. (45)
Rupatadine	10 *vs* 20 mg		Pooled data from 2 DB, RPC, MC	Analysis of pooled data from 2 DB, PC, MC CSU	20 *vs* Plc 0	0.01		Pooled data analysis	High	High	2009	Gimenez-Arnau et al. (49)
Levocetirizine *vs* desloratadine	5, 10, 20 mg	4 weeks	40 Levo, 40 Des	DB/COMP/CO CSU unresponsive to AH single dose	Des 5 *vs* 20 $P = 0.02$, Lev 5 *vs* 20 $P < 0.001$	Des 5 *vs* 20 $P = 0.02$, Lev 5 *vs* 20 $P < 0.001$	Study shows that also switching antihistamine may be beneficial in some patients	None	High	High	2010	Staevska et al. (50)
Desloratadine	5–20 mg Plc	8 weeks	30	DB/CO/Plc Cold urticaria	Yes	0.01 20 *vs* 5 mg		None	High	High	2009	Siebenhaar et al. (51)
Desloratadine	5, 10, 20 mg	6 weeks	15	5 mg ($n = 13$) *vs* escalating 5–10–20 mg is cold urticaria ($n = 28$)	n.a.	0.05 Plc, 20 mg Des *vs* constant dose 5 mg					2012	Magerl et al. (52)
Rupatadine	20 g	2 weeks	21	DB/PC Cross-over	Yes		Complete response in 52%	None			2010	Metz et al. (53)
Various AH	n.a.	n.a.	368	Questionnaire to patients retrospectively			75% of patients reported to have updosed on physician's suggestion themselves with good success	Retrospective				Weller et al. (54)
Various AH	n.a.	n.a.	776	Cross-sectional physician-based survey			25% of physicians use high-dose AH treatment in daily practice as second choice if AH single dose fails	Retrospective				Weller et al. (55)
Bilastine	20, 40, 80 mg	12 weeks	20	DB, RPC, cross-over *P*	Yes	n.a.	Cold urticaria	None	High	High	2012	Krause et al. (56)

AH, antihistamine; ASST, autologous serum skin test; CU, chronic urticaria; COMP, comparison; CSU, chronic spontaneous urticaria; DB, double blind; Des, desloratadine; Levo, levocetirizine; MC, multicenter; PC, *placebo* controlled; Rup, rupatadine; Plc, *placebo*; RPC, randomized *placebo* controlled; n.a., not applicable; n.s., nonsignificant.

Table 18

Investigated study	Study design	*P*-value outcome	Limitations	Inconsistency, indirectness, imprecision	Quality	Importance	Year
Fedorowicz (57)	Cochrane review	n.a.	Based on limited number of studies of mostly ow quality		High	High	2012

n.a., not applicable.

treatment of urticaria (strong recommendation/high level of evidence, accepted with 100%).

Reasoning/summary from discussion. In the previous guidelines, OMA was suggested as add-on treatment to fourfold doses of new-generation oral H1-AHs as a fourth level of treatment in the algorithm. This recommendation is now further supported by high-quality *placebo*-controlled double-blind randomized trials showing efficacy and safety. We thus recommend the use of OMA in those patients not responding to fourfold doses of new-generation oral H1-AHs based on RCTs showing an excellent risk/benefit ratio in this group of patients. There are numerous other case reports that support these observations (65–69).

See Supporting Evidence in Table 20.

Should oral corticosteroids be used in the treatment of urticaria?

We recommend against the long-term use of systemic corticosteroids in urticaria (strong recommendation/high level of evidence, accepted with 99%).

and

We suggest a trial of a short course of systemic corticosteroids in urticaria as third-line therapy or as an option for acute exacerbation (weak recommendation/low level of evidence, accepted with 88%).

Discussed alternatives:

1 We suggest a trial of a short course of systemic corticosteroids in urticaria as third-line therapy (weak recommendation/low level of evidence, voting result, < 50%).
2 We recommend a trial of a short course of systemic corticosteroids in urticaria as third-line therapy (strong recommendation/low level of evidence, voting result, < 50%).
3 We recommend a trial of a short course of systemic corticosteroids in urticaria as third-line therapy or as an option for acute exacerbation (strong recommendation/low level of evidence, voting result, < 50%).

At present, topical corticosteroids are successfully used in many allergic diseases, but in urticaria topical steroids are not helpful (with the possible exception of pressure urticaria on the soles of the feet as alternative therapy with low evidence). If corticosteroids are used, systemic administration at doses between 20 and 50 mg/day is required with inevitable side-effects in the long term. Depending on the country, it must further be noted that steroids are also not licensed for CU (e.g., in Germany, prednisolone is licensed only for acute urticaria). Based on a risk/benefit ratio with other alternative medications being available, we thus recommend against the long-term use of corticosteroids outside specialist clinics (strong recommendation/high quality of evidence). For acute urticaria and acute exacerbations of CSU not responding to modern second-generation AHs, a short course of corticosteroids may, however, be required (in an emergency) and also possibly be beneficial to restore responsiveness to AHs and reduce disease duration warranting a suggestion to use this as an option in the third level.

See Supporting Evidence in Table 21

Should leukotriene antagonists be used in the third-line treatment of urticaria?

We suggest a trial of montelukast as add-on therapy to modern second-generation H1-AHs as third line in the treatment of urticaria (weak recommendation/low level of evidence, accepted with 99%).

Discussed alternatives:

1 We recommend a trial of montelukast as add-on therapy to modern second-generation H1-AHs as third line in the algorithm of treatment of urticaria (strong recommendation/low level of evidence, voting result, 86%).

In the previous guideline, leukotriene receptor antagonists had been recommended as third-line therapy in the algorithm as add-on therapy to modern second-generation H1-AHs based on low-quality evidence. Since then, only one new study and one systematic review have been published favoring this intervention but limiting it to montelukast as add-on therapy to modern second-generation H1-AHs. Based on a risk/benefit ratio with other alternative medications available and comparatively low costs, we thus recommend using montelukast as third-line therapy in the algorithm as add-on to dose fourfold modern second-generation H1-AHs.

See Supporting Evidence in Table 22.

Is dapsone useful in the treatment of urticaria as third-line therapy?

At the present time, it is not possible to give a recommendation for or against treatment with dapsone (accepted with 97%).

Discussed alternatives:

1 We recommend a trial of dapsone as add-on therapy to modern second-generation H1-AHs as third line in the algorithm of treatment of urticaria (strong recommendation/low level of evidence, voting result, 85%).

Reasoning/summary from discussion. In the previous guidelines, dapsone as add-on treatment to fourfold doses of new-generation oral H1-AHs has been suggested as fourth-level

Table 19

Drug	Daily dose	Duration	N active drug/ *placebo*	Study design	$P < 0.05$ *vs* PL	$P < 0.05$ *vs* compared drug	Remarks	Limitations	Quality	Importance	Citation
Cyclosporin	2.5 mg/kg	4 weeks	51 CyA	Controlled	n.a.	n.a.		Not DB, not PC	Low	Low	Serhat Inaloz et al. (58)
Cyclosporin + 20 mg Cet *vs* Plc + 20 mg Cet	4 mg/kg	Initial 4 weeks	20 CyA, 10 Plc	DB PC	Yes	n.a.		0	High	High	Grattan et al. (59)
Cyclosporin + Cet	5 mg/kg + 10 mg Cet	16 weeks		DB PC	Yes	n.a.	Only evaluated as in guideline reports 1 and 3	0	High	High	Vena et al. (60)
Cyclosporin	6 mg/kg	>1 week	3	Uncontrolled	n.a.	n.a.		Uncontrolled, not DB, not PC	Low	Low	Fradin et al. (61)
Cyclosporin	3 mg/kg for 6 weeks, followed by 3 weeks of 2 mg/kg per day, and then 3 weeks of 1 mg/kg per day	6 months	19	Controlled	n.a.	n.a.		Not DB, not PC	Low	Low	Toubi et al. (62)
Cyclosporin	3 mg/kg	8 weeks	7	Retrospective uncontrolled			Only study in children, complete response in all	Retrospective/ small number	Low	High	Doshi and Weinberger (63)
Cyclosporin	1.8 ± 1.1 mg/kg	n/a	68	Retrospective chart review	n.a.	n.a.	>50% complete response	Retrospective, chart review	Low	Low	Hollander et al. (64)

CyA, cyclosporin; DB, double blind; Plc, *placebo*; PC, *placebo* controlled; n.a., not applicable.

Table 20

Urticaria type	Dose	Duration	N active drug/ *placebo*	Study design	$P < 0.05$ *vs* PL	$P < 0.05$ *vs* compared drug	Remarks	Limitations	Quality	Importance	Reference
CSU	Asthma dosing scheme, no minimum total IgE	16 weeks	OMA = 12, Plc = 12	Open, cross-over	Yes	n.a.		Only autologous serum skin test positive	Low	High	Kaplan et al. (70)
CSU	OMA 75–375 mg SC once every 2 or 4 weeks); asthma dosing scheme	24 weeks	OMA = 27, Plc = 22	DB PC	yes	n.a.		Only IgE-anti-TPO + patients	High	High	Maurer et al. (17)
CSU	75 *vs* 300 *vs* 600 mg add-on to H1-antihistamine	4 weeks (+12 weeks of follow-up)	300 mg = 25, 600 mg = 21, 75 mg = 23, *placebo* = 21	DBPC	Yes, for 300 and 600 mg	n.a.		Single dose	High	High	Saini et al. (71)
CSU	300 *vs* 150 *vs* 75 mg	12 weeks (+16 weeks of follow-up)	*N* = 322 (300 mg = 79, 150 mg = 82, 75 mg = 82, *placebo* = 79)	DBPC	Yes, for 150 and 300 mg	n.a.			High	High	Maurer et al. (72)
Cold U	375 mg every 2 weeks	>5 months	1	Uncontrolled		n.a.		Case report			Boyce (73)
Solar U	150 mg every 4 weeks	>4 weeks	1	Uncontrolled		n.a.		Case report	Low	High	Guzelbey et al. (74)
Chol U	300 mg every 2 weeks	>22 weeks	1	Uncontrolled		n.a.		Case report	Low	High	Metz et al. (75)
Delayed pressure U	150 mg every 2 weeks	>3 months	1	Uncontrolled		n.a.		Case report	Low	High	Bindslev-Jensen and Skov (76)
Heat U	450 mg every 2 weeks	>19 months	1	Uncontrolled		n.a.		Case report	Low	High	Bullerkotte et al. (77)
Symptomatic dermographism	300 mg/month	>6 months	2	Uncontrolled		n.a.		Case report	Low	High	Krause et al. (65)
OMA	0.016 mg/kg/l U/ml per month	4 weeks	12	Controlled, single blind	yes	n.a.		Single blind	Low	High	Kaplan et al. (70)
OMA	75–375 mg, dose determined by using the approved asthma dosing table once every 2 or 4 weeks	24 weeks	27 OMA, 22 Plc	Multicenter, RDBPC study	yes	n.a.					Maurer et al. (17)

CSU, chronic spontaneous urticaria; OMA, omalizumab; RDBPC, randomized double blind *placebo* controlled; Plc, *placebo*; DBPC, double blind, *placebo* controlled; PC, *placebo* controlled; n.a., not applicable.

Table 21

Drug	Daily dose	Duration	N active drug/*placebo*	Study design	$P < 0.05$ *vs* PL	$P < 0.05$ *vs* compared drug	Remarks	Limitations	Quality	Importance	Year	Citation
Prednisone	25 mg/day on days 1, 2, and 3; 12.5 mg/day on days 4, 5, and 6; and 6.25 mg/day on days 7, 8, 9, and 10	10 days	90	Open	n.a.	n.a.	Included only patients refractory to standard doses of ns H1-AHs. In 40/86 patients (47%), prednisone induced remission of the disease and subsequent control with AH at licensed doses only. Thirty-five patients responded well but relapsed when prednisone doses were tapered or shortly after withdrawal	retrospective uncontrolled	Low	High	2010	Asero and Tedeschi (78)

AH, antihistamine; n.a., not applicable.

Table 22

Drug	Daily dose	Duration	N active drug/ *placebo*	Study design	$P < 0.05$ *vs* PL	$P < 0.05$ *vs* compared drug	Remarks	Limitations	Quality	Importance	Year	Citation
Montelukast *vs* Cet on demand *vs* Plc + Cet on demand	10 mg (cetirizine 10 mg on demand, also in Plc group)	6 weeks each	15 each group	SB PC CRO	Yes	n.a.	2-week wash-out period between cross-over	Single blind, low number	Low	High	2002	Erbagci (79)
Mont + Des *vs* Plc + Des *vs* Plc	10 mg + DLOR 5 mg	6 weeks	25 Des + Plc; 26 Des + Mont 25 Plc + Plc	DB PC	Yes	Yes	1-week PL run-in, 1-week PL-wash-out phase; example of combination therapy AH + antileukotriene	Low number of patients	High	High	2004	Nettis et al. (80)
Des, montelukast single or combination *vs placebo*	5 Des, 10 months	6 weeks (8 weeks later follow-up)	120, 40	DB PC Parallel groups	Des *vs* Plc < 0.01, Mont *vs* Plc < 0.01, Des + Mont *vs* Plc < 0.01, on TSS (total symptom score)	Des *vs* Mont < 0.01	Des and Mont both had excellent safety	Low number of patients	High	High	2004	Di Lorenzo et al. (81)
ZAF	2 × 20 mg	6 weeks	46 in cross-over	DB PC CRO	No	n.a.	No subgroup with benefit could be identified	0	High	High		Reimers et al. (82)
Cetirizine monotherapy *vs* cetirizine combination with ZAF	10 mg Cet (2 × 20 mg ZAF plus cetirizine 10 mg, diphenhydramine)	3 weeks	48, 47	DB PC MC	Yes combination Cet + ZAF superior to Cet monotherapy	n.a.	Only patients resistant to prior run-in phase with Cet 10 mg/day were randomized; only ASST + CSU refractory to H1-AH monotherapy showed a benefit from the addition of ZAF to Cet	0	High	High	2004	Bagenstose et al. (83)
Symptoms and QoL												
10 mg montelukast as add-on to single dose ns antihistamine	10 mg	3 weeks	22, Plc = n	DB PC cross-over add-on	yes, montelukast as add-on to AHs	n.a.	In small number of patients, standard dose of antihistamine was not standardized but prescribed AH was continued in patients refractory to AH treatment	0	High	High		Kosnik and Subic (84)
Systematic review	n.a	n.a	n.a	n.a	Yes, montelukast as add-on to AHs	n.a	Covers literature only until 2009		High	High		Di Lorenzo et al. (85)

PC, *placebo* controlled; CRO, cross-over; DB, double blind; Plc, *placebo*; Cet, cetirizine; Des, desloratadine; Mont, montelukast; ASST, autologous serum skin test; AH, antihistamine; n.a., not applicable; ZAF, zafirlukast; CSU, chronic spontaneous urticaria.

treatment in the algorithm. This recommendation was based on previous open RCTs showing a good risk/benefit ratio in this group of patients but put emphasis on low costs and worldwide availability. Although these arguments have not changed for the intervention on level 3, the level of evidence for other interventions in level 3 has increased. Therefore in comparison, the level of evidence for dapsone was too low to keep it in level 3. Before reaching a decision for or against dapsone, further trials of high quality are needed.

See Supporting Evidence in Table 23.

Should the same treatment algorithm be used in children?

We suggest the same treatment algorithm to be used in children with CU (weak recommendation/clinical consensus, accepted with 100%).

Discussed alternatives:

1 We recommend the same treatment algorithm to be used in children with CU (strong recommendation/clinical consensus, voting result, 91%).

Reasoning/summary from discussion. Already in previous guidelines, the same algorithm has been suggested to be used in children, with the remark that high-quality evidence was only available for the first line of treatment with modern second-generation AHs. Those are also licensed in children. The lack of evidence is based on the fact that urticaria is rare in children and that those children who suffer from urticaria have less severe symptoms than many adults. Due to the low number of affected children, high-quality randomized trials are thus not feasible and none have been published so far on the level 2–4 treatment strategies except for one study with cyclosporin. Anyhow all drugs have been used and are licensed in children in other indications showing their safety. Based on this knowledge, it appeared to be the best suggestion to be offered to use the same algorithm for children.

See Supporting Evidence in Table 24.

Should the same treatment algorithm be used in pregnant women and during lactation?

We suggest the same treatment algorithm be used in pregnant women and during lactation in urticaria (weak recommendation/clinical consensus, accepted with 97%).

Discussed alternatives:

1 We recommend the same treatment algorithm be used in pregnant women and during lactation in urticaria (strong recommendation/clinical consensus, voting result, 85%).

Reasoning/summary from discussion. Already in previous guidelines, the same algorithm has been suggested for use in pregnant or lactating women, with the remark that high-quality evidence was only available for the first line of treatment with modern second-generation AHs. Among these, loratadine has the best published safety record. The relative lack of evidence is based on the fact that high-quality randomized trials are not ethical and none have been published so far on alternative treatment strategies. The available safety data on loratadine are based on retrospective observations in women with allergic rhinitis but the safety data may well be extrapolated. Extrapolation of safety data can also be made for treatment options in levels 2–4 where drugs have been used in other indications. Based on this knowledge, it

Table 23

Drug	Daily dose	Duration	N active drug/ *placebo*	Study design	$P < 0.05$ *vs* PL	$P < 0.05$ *vs* compared drug	Remarks	Limitations	Quality	Importance	Year	Citation
Dapsone plus desloratadine *vs* desloratadine	50 mg dapsone + 5 mg desloratadine	12 weeks	38 Dap + 27 Des, Plc + Des	Open randomized controlled	n.a.	0.001		Open study	Low	High	2008	Engin and Ozdemir (86)

Dap, dapsone; Des, desloratadine; Plc, *placebo*; n.a., not applicable.

Table 24

Investigated study	Study design	*P*-value outcome	Limitations	Inconsistency, indirectness, imprecision	Quality	Importance	Year	Citation
Cyclosporin in children with CSU refractory to AH	Open	n.a.	7 patient case reports	n.a.	Low	High	2009	Doshi and Weinberger (63)

CSU, chronic spontaneous urticaria; AH, antihistamine; n.a., not applicable.

appeared to be the best suggestion to use the same algorithm for pregnant and lactating women in levels 1, 2, and 3. The decision must be made on individual basis.

Are pseudoallergen-free diets useful in the extended diagnostic program of CSU?

We recommend the use of pseudoallergen-free diets (N.B. the term in pseudoallergen-free diet is most widely used as the term suggested by official EAACI nomenclature is too long: nonallergic hypersensitivity reaction causing agent-free diet) in the extended diagnostic program of CSU in patients with daily or almost daily symptoms only (strong recommendation/high-quality evidence, accepted with 100%).

and

We suggest to use pseudoallergen-free diet in the management program only for those patients responding to the diet (weak recommendation/high-quality evidence, accepted with 89%).

Discussed alternatives:

1 We recommend the use of pseudoallergen-free diets in the extended diagnostic program of CSU (strong recommendation/high-quality evidence, voting result, 72%).
2 We recommend the use of pseudoallergen-free diets in the extended diagnostic and management program of CSU in patients with daily or almost daily symptoms only (strong recommendation/high-quality evidence, voting result, $< 50\%$).
3 We recommend the use of pseudoallergen-free diets in the extended diagnostic and management program of CSU in patients with daily or almost daily symptoms only (strong recommendation/high-quality evidence, voting result, $< 50\%$).
4 We suggest the use of pseudoallergen-free diets in the extended diagnostic and management program of CSU in patients with daily or almost daily symptoms only (weak

Table 25 Studies investigated in guidelines version 2009

Author(s)	Disease studied	Number of patients	Positive reactions to food additives	Provocation	Improvement on diet
Warin and Smith (87)	Chronic urticaria	111	59.5% (incl. ASS)	Single blind, *placebo* controlled	75%
Genton et al. (88)	Chronic urticaria	17	88.2% (incl. ASS)	Single blind	93.3%
Michaelsson and Juhlin (89)	Chronic urticaria and angioedema	52	75% (incl. ASS)	Single blind	81.3% free of symptoms 6.3% improvement
Thune and Granhold (90)	Chronic urticaria	100	62% (incl. ASS)	Single blind	80.6% improvement 19.4% spontaneous improvement
Wüthrich and Fabro (91)	Urticaria	620	26.6% (incl. ASS)	Single blind	Over 60% improvement
Juhlin (92)	Chronic urticaria and angioedema in 9%	330	31%	Single blind	No data
Ortolani et al. (93)	Chronic urticaria	70	59.6% (incl. ASS)	Single blind, *placebo* controlled	No data
Rudzki et al. (94)	Chronic urticaria	158	31.6%		No data
Ros et al. (95)	Chronic urticaria	75		Follow-up study	24% free of symptoms 57% improvement
Verschave et al. (96)	Chronic urticaria	67	No		55% of all patients
Gibson and Clancy (97)	Chronic urticaria	76	Up to 54%	Single blind, *placebo* controlled	71.1% free of symptoms 19.7% improvement 9.2% refused diet of all patients
Kirchhof et al. (98)	Chronic intermittent urticaria	100	39%	DB, *placebo* controlled	44%
Supramaniam and Warner (99)	Urticaria and angioedema in 74.4%	43	24%	DB, *placebo* controlled	87.5%
Zuberbier et al. (100)	Chronic urticaria and/or angioedema	67	19%	DB, *placebo* controlled	73% of all patients
Pigatto and Valsecchi (101)	Chronic urticaria	202 of 348	37.3%	DB, *placebo* controlled	62.4% improvement 17.3% no improvement 20.3% discontinued diet of all patients

ASS, acetylsalicylic acid.

recommendation/high-quality evidence, voting result, < 50%).

Already in the previous guidelines, pseudoallergen-free diets have been recommended as part of the extended diagnostic program in CSU. This recommendation was already based on high-quality evidence but limited to only patients with CSU with daily or nearly daily symptoms. High quality was mainly based on controlled open studies but dietary intervention does not easily allow a DB PC setting. Since then, further studies showing the benefit of pseudoallergen-free diets in a subset of the urticaria patients have been published also in other cultural groups (Turkey). We recommend the use of pseudoallergen-free diets in the extended diagnostic program of CSU (strong recommendation/high-quality evidence).

See Supporting Evidence in Tables 25–26.

Should modern second-generation AHs be taken regularly or as needed?

We recommend modern second-generation oral H1-AHs be taken continuously in the lowest necessary dose rather than on demand (strong recommendation/high-quality evidence, voting result, accepted with 98%).

Discussed alternatives:

1 We recommend modern second-generation oral H1-AHs be taken regularly and not as needed (strong recommendation/high-quality evidence, voting results, < 90%).
2 We recommend modern second-generation oral H1-AHs be taken continuously and not as needed (strong recommendation/high-quality evidence, voting results, < 90%).
3 We recommend modern second-generation oral H1-AHs be taken continuously in the lowest necessary dose and not as needed (strong recommendation/high-quality evidence, voting results, < 90%).

Reasoning/summary from discussion. The recommendation to take new-generation oral H1-AHs that do not cause sedation regularly and not as needed is based on low-quality evidence of one trial comparing both treatment options (104) but on high circumstantial evidence, because it (i) could be shown that modern second-generation AHs can suppress occurrence of new wheals and angioedema but not reduce time to spontaneous recovery of already existing wheals (105), (ii) high-quality evidence of good safety data and better QoL of patients while putting less emphasis on costs.

See Supporting Evidence in Table 27.

Should different H1-AHs be used at the same time?

We recommend preferably to updose modern second-generation oral H1-AHs that do not cause sedation up to fourfold (strong recommendation/high-quality evidence) instead of combining different H1-AHs at the same time (strong recommendation/low-quality evidence, accepted with 100%).

Reasoning/summary from discussion. We recommend preferably updosing with new-generation oral H1-AHs that do not

Table 26 Studies published since 2009

Study design	*P*-value outcome	Limitations	Quality	Importance	Year	Citation
Prospective, open	n.a. 41% responder rate, *n* = 34	Controlled, open	High	High	2012	Akoglu et al. (102)
Prospective, open	n.a. 34% responder rate, *n* = 140	Controlled, open	High	High	2010	Magerl et al. (103)

n.a., not applicable.

Table 27

Investigated study	Study design	*P*-value outcome	Limitations	Quality	Importance	Year	Citation
Observation of resolution of wheals under different treatment options	Prospective, DB 5 *vs* 20 mg Des, *n* = 29	n.a.	Indirect high-quality evidence study showed that AH treatment could not enhance the resolution of already existing wheals at the time of administration on demand	High	High	2012	Weller et al. (105)
Comparison of AH regularly on demand	Randomized, double-blind, parallel group study, *n* = 46	>0.05		High	High	2008	Grob et al. (104)

Des, desloratadine; AH, antihistamine; n.a., not applicable.

Table 28

Investigated study	Study design	*P*-value outcome	Limitations	Inconsistency, indirectness, imprecision	Quality	Importance	Year	Citation
	2 × 2 *vs* 3 × 2 *vs* 4 × 1 retrospective	Plc 0.01, 2 × 2 *vs* other treatments	Retrospective, small number	None	High	High	2009	Schulz et al. (106)

Plc, *placebo*.

Table 29

Investigated study	Study design	*P*-value outcome	Limitations	Inconsistency, indirectness, imprecision	Quality	Importance	Year	Citation
	S3 level guideline	n.a.	None		High	High	2009	Zuberbier et al. (2)

n.a., not applicable.

cause sedation up to fourfold (strong recommendation/high-quality evidence) instead of mixing different H1-AHs at the same time, which has been proposed as this procedure is not off-label if licensed doses are used in contrast to updosing. This recommendation is based on the fact that updosing has been proven to be efficacious in RCTs which are missing for the alternative concept of mixing different H1-AHs. In a retrospective comparison, it was shown that updosing is superior to combining (low-quality evidence) as well as circumstantial evidence that different H1-AHs also exert other anti-inflammatory properties that are different from those preventing histamine receptor stimulation. These properties can be improved with updosing (low-quality evidence). In summary, updosing is better than mixing (strong recommendation/low-quality evidence).

See Supporting Evidence in Table 28.

If there is no improvement, should higher than fourfold doses of H1-AHs be used?

We recommend preferably updosing with modern second-generation H1-AHs that do not cause sedation up to fourfold and to not further increase the dose (strong recommendation/low-quality evidence, accepted with 99%).

Reasoning/summary from discussion. This recommendation is based on the fact that updosing has previously been recommended in the guideline and has been proven to be efficacious and safe in RCTs for up to fourfold doses (see question 12) but studies are completely missing for the use of higher doses in urticaria.

See Supporting Evidence in Table 29.

External review

All societies involved in the consensus meeting were invited to comment on the final document within a timeframe of 4 weeks. No response was considered as approval. The IADVL had a number of specific comments regarding the specialties in the medical system of India. These were published in the guideline. The AAAAI participated in the process of developing these guidelines with input, review, and thoughtful comments, anyhow is not an endorsing founder society.

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Future updates of the guidelines

The validity of these guidelines is 4 years (2016). Because new interventions may be licensed or relevant changes in information (e.g., on adverse events) may become available before this point, the steering committee will evaluate the need for an earlier update of the whole guidelines or individual questions at regular intervals.

Conflicts of interest

Conflict of interests were declared by all participants prior to the consensus conference. They were assessed by the steering committee with respect to their acceptability. The assessment of the individual declaration of possible conflicting interests did not lead to the exclusion of any of the panel members. All panel members declared that they feel that their possible conflict of interests will not interfere in a relevant way with their voting behavior.

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