

Definition, aims, and implementation of GA²LEN/HAEi Angioedema Centers of Reference and Excellence

To the Editor,

GA²LEN, the Global Allergy and Asthma European Network, and HAE international (HAEi), the global umbrella organization for the world's hereditary angioedema (HAE) patient groups, have launched their joint ACARE (Angioedema Center of Reference and Excellence) program, within GA²LEN's center of reference and excellence (CORE) initiative. Angioedema is a common, heterogeneous, often debilitating and chronic condition and is frequently a challenge for physicians and affected patients, especially patients suffering from recurrent attacks. Additionally, it can be a challenge for some patients to understand the underlying etiology of their angioedema (Table 1). GA²LEN's CORE networks, such as UCARE for urticaria and ADCARE for atopic dermatitis, help to improve the management of difficult-to-treat conditions. Here, we describe the aims, requirements, provisions, application process, audit, and accreditation protocol for GA²LEN/HAEi ACAREs. ACAREs aim to provide excellence in angioedema management, increase the knowledge of angioedema through research and education, and promote advocacy activities that raise angioedema awareness. To become a certified ACARE, angioedema centers must fulfill 32 requirements, defined by specific provisions that will be assessed during an audit visit. The ACARE program will result in a strong network of angioedema specialists, promote angioedema research and awareness, and harmonize and improve angioedema management globally. ACAREs will

expand access to modern angioedema medicines in countries where they are available and help to bring them to countries where they are not.¹

This document summarizes the aims of GA²LEN/HAEi Angioedema Centers of Reference and Excellence (ACAREs) and elaborates the requirements that ACAREs must fulfill to become certified. It also provides (see Appendix S1) background information on GA²LEN and HAEi, including HAEi member organizations and regional patient advocates, on why we need an Angioedema Center of Reference and Excellence (ACARE) program and network, and on the accreditation and certification process, governance and funding, and on the interaction with other GA²LEN networks of centers of reference and excellence. The protocols, aims, requirements, and provisions related to becoming a certified ACARE are based on (a) the experience of the GA²LEN UCARE network and (b) input from angioedema patients, general practitioners, and angioedema specialists.

What are the aims of GA²LEN/HAEi ACAREs? The aims of ACAREs are to set the global standard for excellence in comprehensive angioedema care through research, education, advocacy, and interaction among ACAREs. By serving as referral centers for the diagnosis and management of patients with angioedema, ACAREs will complement the local healthcare system. ACAREs aim to increase knowledge and awareness of angioedema.

TABLE 1 Classification of angioedema

Bradykinin-mediated angioedema				Mast cell mediator-mediated angioedema		Unknown mediator
C1-INH deficiency/defect		C1-INH normal		IgE mediated	Non-IgE mediated	
Inherited	Acquired	Inherited	Acquired			
HAE-1	AAE-C1-INH	HAE nC1-INH (HAE-FXII, HAE-ANGPT1, HAE-PLG, HAE-KNG1, HAE-UNK)	AE due to medication that interferes with BK degradation, eg ACEi	Angioedema with or without wheals in patients with urticaria	Angioedema with or without wheals in patients with urticaria	Idiopathic AE
HAE-2				Anaphylaxis		

Abbreviations: AAE-C1-INH, acquired angioedema due to C1-inhibitor deficiency; ACEi-AE, angiotensin-converting enzyme inhibitor-induced angioedema; BK, bradykinin; HAE nC1-INH, hereditary angioedema with normal C1-inhibitor levels, either due to a mutation in factor XII (F12), angiotensin-converting enzyme 1 (ANGPT1), plasminogen (PLG), kininogen-1 (KNG1), or unknown (UNK) (HAE-FXII, HAE-ANGPT1, HAE-PLG, HAE-KNG1, HAE-UNK); HAE-1, hereditary angioedema due to C1-inhibitor deficiency; HAE-2, hereditary angioedema due to C1-inhibitor dysfunction.

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Audit Date: _____ Head of the Center: _____
Audited Center: _____
Auditor: _____ Deputy Head: _____
Last audit: _____

Requirement	Information / Not up	Information	Yes/No	Yes
1. Personnel training or education	Center needs to be a hospital or affiliated with a hospital with explicit facilities to allow for continuous training of personnel in the management of angioedema.	Center needs to be a hospital or affiliated with a hospital with explicit facilities to allow for continuous training of personnel in the management of angioedema.	☐	☐
2. Personnel skills and other factors	Center needs to have staff with specific training and experience in the management of angioedema.	Center needs to have staff with specific training and experience in the management of angioedema.	☐	☐
3. Open to children and adult patients	Center needs to be able to provide care for angioedema patients of any age, either by having a dedicated unit or by having a dedicated unit.	Center needs to be able to provide care for angioedema patients of any age, either by having a dedicated unit or by having a dedicated unit.	☐	☐
4. Team of professionals with specific angioedema training	Center needs to have a team of professionals with specific angioedema training.	Center needs to have a team of professionals with specific angioedema training.	☐	☐
5. Multidisciplinary approach	Center needs to be able to interact with other specialists in the management of angioedema.	Center needs to be able to interact with other specialists in the management of angioedema.	☐	☐
6. Accessibility and visibility	Angioedema patients need to be able to find the center via information in the web, center needs to have a specific website for angioedema patients.	Angioedema patients need to be able to find the center via information in the web, center needs to have a specific website for angioedema patients.	☐	☐
7. Communication skills	Center staff needs to be able to communicate with angioedema patients in a clear and understandable way.	Center staff needs to be able to communicate with angioedema patients in a clear and understandable way.	☐	☐
8. Quality management	Center needs to have Quality Management (QM) system in place.	Center needs to have Quality Management (QM) system in place.	☐	☐
9. Structural documentation	Center needs to have a system to document the management of angioedema patients.	Center needs to have a system to document the management of angioedema patients.	☐	☐
10. Critical incidents reporting and case management	Center needs to have a system to report critical incidents and manage them.	Center needs to have a system to report critical incidents and manage them.	☐	☐
11. Assessment of critical incidents	Center needs to have a system to assess critical incidents and manage them.	Center needs to have a system to assess critical incidents and manage them.	☐	☐
12. Research and innovation	Center needs to have a system to research and innovate in the management of angioedema.	Center needs to have a system to research and innovate in the management of angioedema.	☐	☐
13. Support of the ACARE network	Center needs to have a system to support the ACARE network.	Center needs to have a system to support the ACARE network.	☐	☐
14. Newer gene of attitude	Center needs to have a system to support the ACARE network.	Center needs to have a system to support the ACARE network.	☐	☐

(B)

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The GALEN ACARE office hereby certifies that the Department and Center Name _____ and for Name of Head of Center: City: Country _____ has been externally audited and fulfills the GALEN HAEi quality criteria as a GALEN HAEi Angioedema Center of Reference and Excellence (GALEN HAEi ACARE).

Date: 02/02/2019 Valid until: 02/02/2021

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FIGURE 1 A and B, Audit checklist for GA²LEN/HAEi Angioedema Center of Reference and Excellence (ACARE) certification (A) and certificate awarded to GA²LEN/HAEi ACAREs upon a successful audit (B). A, The list shows and explains the requirements for becoming a GA²LEN/HAEi ACARE and the deliverables that are reviewed during the audit process. B, The certificate is awarded for 2 y and requires successful re-audit to be extended

What are the requirements for GA²LEN/HAEi ACAREs? ACAREs are required to demonstrate excellence in the management of angioedema, research activities, efforts in education, and advocacy activity. ACAREs need to fulfill 32 requirements, which are explained in the audit checklist (Figure 1A). This checklist includes specific deliverables for each requirement. For example, the requirement to know and follow international guidelines and consensus documents for angioedema (Requirement #16) entails that physicians and other ACARE healthcare professionals have read and understood the current versions of these guidelines and consensus documents and that their recommendations are implemented in their center.

These guidelines and consensus documents include, for example, the international WAO/EAACI guideline for HAE, the EAACI/GA²LEN/EDF/WAO guideline for urticaria, the International/Canadian hereditary angioedema guideline,²⁻⁵ the international consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency, the international consensus on the use of genetics in the management of HAE,⁶ and the international consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency.⁷ The deliverables for this requirement are that (a) current guideline and consensus document versions are present (paper or electronic version) at the center, (b) ACARE staff can answer questions on the recommendations these documents provide, and (c) ACARE physicians can show, upon request, by use of a patient file, that patient management decisions are based on guideline recommendations (Figure 1B).

This publication marks our intent to start the implementation of the GA²LEN/HAEi ACARE initiative. Specialty centers for angioedema have started to apply to become ACAREs, and audits and certifications are ongoing (Figure 1B). We expect that most GA²LEN UCARE centers and many angioedema specialty centers will become ACAREs in the near future. We predict and hope that by 2022, GA²LEN/HAEi ACAREs will be established in every continent. This will result in a strong global network of angioedema specialists, promote angioedema research, and harmonize and improve angioedema management worldwide. GA²LEN and HAEi will measure the impact of ACAREs over time and document and report the benefits of this initiative. ACARE network activities and a current list of ACAREs are posted on the network's website (www.acare-network.com).

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other from Shire HGT, personal fees and other from Pharming NV, outside the submitted work. Dr Campos reports and Personal fees for consulting and lectures from Takeda. Dr Cancian served for Scientific Advisory Boards, and received travel grants, for/from CSL Behring and Shire-Takeda. His Institution (Department of Medicine, University of Padua, Italy) received grants from CSL Behring and Shire-Takeda. Dr Cohn reports personal fees from Takeda, personal fees from Pharming, personal fees from CSL, personal fees from BioCryst, outside the submitted work. Dr Craig reports grants, personal fees and other from CSL Behring, grants and personal fees from Dyax, grants, personal fees and other from Takeda, grants and personal fees from BioCryst, grants and personal fees from Pharming, personal fees from Grifols, grants and non-financial support from GSK, grants and non-financial support from Regeneron, grants and non-financial support from Novartis/Genentech, outside the submitted work; and On the Medical Advisory Board for HAE-A of America, AAAAI Board, ALA Mid Atlantic Board. Dr Dissemmond reports grants and personal fees from Novartis, outside the submitted work. Dr Du-Thanh reports personal fees from SHIRE/T. Dr Ensina reports personal fees from NOVARTIS, personal fees and non-financial support from TAKEDA, personal fees from SANOFI, outside the submitted work. Dr Farkas reports grants and personal fees from CSL Behring, grants and personal fees from Shire/Takeda, grants and personal fees from Pharming, personal fees from BioCryst, personal fees from Kalvista, outside the submitted work. Dr Gimenez-Arnau reports grants and personal fees from URIACH, grants and personal fees from NOVARTIS, personal fees from DSANOFI, grants from CARLOS III FEDER, personal fees from FAES, personal fees from GSK, personal fees from ALMIRALL, personal fees from ASTRA ZENECA, outside the submitted work. Dr Fukunaga reports personal fees from A Takeda company (Shire), personal fees from CSL Behring, outside the submitted work. Dr Gompels reports other from Speaker at Novartis Urticaria conference 2019, outside the submitted work; and A member of the Immunology Clinical reference group. Dr Gower reports grants, personal fees, research grants and other from Takeda/Shire/Dyax, research grants and other from BioCryst Pharmaceuticals, other from CSL Behring, other from Pharming, other from Fresenius kabi, outside the submitted work. Dr Grumach reports grants, personal fees and other from Shire/Takeda, personal fees and other from CSL Behring, outside the submitted work. Dr Hide reports grants and personal fees from Shire/Takeda, Mitsubishi-Tanabe, Taiho-yakuhin, personal fees from CSL-Behring, BioCryst, Novartis, Teikoku-Seiyaku, Eizai, Kaken, Kyowahakkou-Kirin, grants from Glaxo-Smith-Klein, outside the submitted work. Dr Jakob reports grants, personal fees and non-financial support from Novartis, personal fees and non-financial support from Thermo Fisher Scientific, grants and personal fees from ALK-Abello, personal fees from Celgene, personal fees and non-financial support from Bencard/Allergy Therapeutics, personal fees from Allergopharma, outside the submitted work. Dr Kaplan reports other from Genentech, other from Novartis, other from Sanofi Aventis, other from BioCryst, outside the submitted work. Dr Katelaris reports grants and personal fees from CSL Behring, grants and personal fees

from Takeda, grants from BioCryst, during the conduct of the study. Dr Kleinheinz reports personal fees from Novartis, during the conduct of the study; personal fees from Abbvie, personal fees from Leo GmbH, personal fees from Janssen, personal fees from Medac, personal fees from Galderma, personal fees from Celgene, personal fees from Bencard, outside the submitted work. Dr Kocatürk reports personal fees from Novartis, personal fees from Sanofi, outside the submitted work. Dr Longhurst reports grants and personal fees from BioCryst, grants, personal fees and non-financial support from CSL Behring, grants from Ionis, grants from Kalvista, personal fees from Pharming, grants, personal fees and non-financial support from Takeda, personal fees from GSK, personal fees from Octapharma, outside the submitted work. Dr MacGinnitie reports personal fees from BioCryst, personal fees from Shire, outside the submitted work. Dr Magerl reports personal fees from CSL Behring, personal fees from Shire/part of Takeda, personal fees from Novartis, personal fees from BioCryst, personal fees from KalVista, personal fees from Pharming, outside the submitted work. Dr Makris reports personal fees from Novartis, outside the submitted work. Dr Marsland reports grants and personal fees from Novartis, personal fees and non-financial support from Sanofi, personal fees from Galderma, personal fees from Roche, non-financial support from Almirall, outside the submitted work. I. Martinez Saguer has received honoraria, research funding, and travel grants from BioCryst, CSL Behring, Pharming, and Takeda/Shire, KalVista and/or served as a consultant and/or participated in advisory boards for these companies. Dr Metz reports personal fees from Moxie, personal fees from Novartis, personal fees from Roche, personal fees from Sanofi, personal fees from Shire, outside the submitted work. Dr Papadopoulos reports personal fees from Novartis, personal fees from Nutricia, personal fees from HAL, personal fees from MENARINI/FAES FARMA, personal fees from SANOFI, personal fees from MYLAN/MEDA, personal fees from BIOMAY, personal fees from AstraZeneca, personal fees from GSK, personal fees from MSD, personal fees from ASIT BIOTECH, personal fees from Boehringer Ingelheim, grants from Gerolymatos International SA, grants from Capricare, outside the submitted work. Dr Reich reports personal fees from Abbvie, personal fees from Bioderma, personal fees from Chema Elektromet, personal fees from Galderma, personal fees from Bausch Health, personal fees from Janssen, personal fees from Leo Pharma, personal fees from Medac, grants and personal fees from Menlo Therapeutics, personal fees from Novartis, personal fees from Pierre-Fabre, personal fees from Trevi, personal fees from Kymab Limited, personal fees from MSD, personal fees from Metriopharm, personal fees from Drug Delivery Solutions, personal fees from Eli Lilly, outside the submitted work. Dr Riedl reports grants and personal fees from CSL Behring, grants and personal fees from Shire/Takeda, grants and personal fees from BioCryst, grants and personal fees from Pharming, personal fees from Pharvaris, personal fees from Adverum, personal fees from KalVista, personal fees from Attune, grants from Ionis, outside the submitted work; and US HAEA Medical Advisory Board Member - uncompensated. Dr Röckmann-Helmbach reports other from Pharming, during the conduct of the

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Kryolan, personal fees from L'Oréal, outside the submitted work; and Organizational affiliations: Üommittee member: WHO-Initiative "Allergic Rhinitis and Its Impact on Asthma" (ARIA) Member of the Board: German Society for Allergy and Clinical Immunology (DGAKI) Dead: European Centre for Allergy Research Foundation (ECARF) Decretary General: Global Allergy and Asthma European Network (GA2LEN) Member: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO). Other authors declare that they have no conflicts of interest.

Marcus Maurer¹ 
 Werner Aberer²
 Rosana Agondi³
 Mona Al-Ahmad⁴ 
 Maryam Ali Al-Nesf⁵ 
 Ignacio Ansotegui⁶
 Rand Arnaout⁷
 Luisa Karla Arruda⁸ 
 Riccardo Asero⁹ 
 Emel Aygören-Pürsün¹⁰
 Aleena Banerji¹¹
 Andrea Bauer¹²
 Moshe Ben-Shoshan¹³
 Alejandro Berardi¹⁴
 Jonathan A. Bernstein¹⁵ 
 Stephen Betschel¹⁶
 Carsten Bindslev-Jensen¹⁷
 Mojca Bizjak¹⁸ 
 Isabelle Boccon-Gibod¹⁹
 Konrad Bork²⁰ 
 Laurence Bouillet¹⁹ 
 Henrik Balle Boysen²¹
 Nicholas Brodzski²²
 Sigurd Broesby-Olsen¹⁷ 
 Paula Busse²³
 Thomas Buttgerit¹
 Anette Bygum²⁴ 
 Teresa Caballero²⁵
 Régis A. Campos^{26,27}
 Mauro Cancian²⁸
 Ivan Cherrez-Ojeda^{29,30} 
 Danny M. Cohn³¹
 Célia Costa³²
 Timothy Craig³³
 Paulo Ricardo Criado^{34,35,36}
 Roberta F. Criado³⁷
 Dorottya Csuka³⁸
 Joachim Dissemond³⁹
 Aurélie Du-Thanh⁴⁰
 Luis Felipe Ensina⁴¹
 Ragıp Ertaş⁴²
 José E. Fabiani⁴³
 Claudio Fantini⁴⁴

Henriette Farkas³⁸ 
 Silvia Mariel Ferrucci⁴⁵
 Ignasi Figueras-Nart⁴⁶
 Natalia L. Fili⁴⁷ 
 Daria Fomina^{48,49}
 Atsushi Fukunaga⁵⁰ 
 Asli Gelincik⁵¹ 
 Ana Giménez-Arnau⁵² 
 Kiran Godse⁵³
 Mark Gompels⁵⁴
 Margarida Gonçalves⁵⁵
 Maia Gotua⁵⁶ 
 Richard Gower⁵⁷
 Anete S. Grumach⁵⁸
 Guillermo Guidos-Fogelbach⁵⁹
 Michihiro Hide⁶⁰
 Natalia Ilina⁶¹
 Naoko Inomata⁶²
 Thilo Jakob⁶³
 Dario O. Josviack⁶⁴
 Hye-Ryun Kang⁶⁵ 
 Allen Kaplan⁶⁶ 
 Alicja Kasperska-Zajac⁶⁷ 
 Constance Katelaris⁶⁸
 Aharon Kessel⁶⁹
 Andreas Kleinheinz⁷⁰
 Emek Kocatürk⁷¹
 Mitja Košnik¹⁸ 
 Dorota Krasowska⁷²
 Kanokvalai Kulthanan⁷³
 M. Sendhil Kumaran⁷⁴
 José Ignacio Larco Sousa⁷⁵
 Hilary J. Longhurst^{76,77,78}
 William Lumry⁷⁹
 Andrew MacGinnitie⁸⁰ 
 Markus Magerl¹
 Michael P. Makris⁸¹
 Alejandro Malbrán⁸²
 Alexander Marsland⁸³
 Inmaculada Martinez-Saguer⁸⁴
 Iris V. Medina⁸⁵
 Raisa Meshkova⁸⁶
 Martin Metz¹ 
 Iman Nasr⁸⁷ 
 Jan Nicolay⁸⁸
 Chikako Nishigori⁸⁹
 Isao Ohsawa⁹⁰
 Kemal Özyurt⁹¹
 Nikolaos G. Papadopoulos⁹² 
 Claudio A. S. Parisi⁹³
 Jonathan Grant Peter⁹⁴
 Wolfgang Pfützner⁹⁵ 
 Todor Popov⁹⁶

- Nieves Prior⁹⁷
German D. Ramon⁹⁸
Adam Reich⁹⁹
Avner Reshef¹⁰⁰ 
Marc A. Riedl¹⁰¹ 
Bruce Ritchie¹⁰²
Heike Röckmann-Helmbach¹⁰³
Michael Rudenko¹⁰⁴
Andaç Salman¹⁰⁵ 
Mario Sanchez-Borges¹⁰⁶ 
Peter Schmid-Grendelmeier¹⁰⁷ 
Faradiba S. Serpa¹⁰⁸
Esther Serra-Baldrich¹⁰⁹
Farrukh R. Sheikh¹¹⁰
William Smith¹¹¹
Angèle Soria¹¹² 
Petra Staubach¹¹³
Urs C. Steiner¹¹⁴
Marcin Stobiecki¹¹⁵
Gordon Sussman¹¹⁶ 
Anna Tagka¹¹⁷ 
Simon Francis Thomsen¹¹⁸ 
Regina Treudler¹¹⁹
Solange Valle¹²⁰
Martijn van Doorn¹²¹
Lilian Varga³⁸ 
Daniel O. Vázquez¹²² 
Nicola Wagner¹²³
Liangchun Wang¹²⁴ 
Christina Weber-Chrysochoou¹⁰⁷
Young-Min Ye¹²⁵ 
Anna Zalewska-Janowska¹²⁶
Andrea Zanichelli¹²⁷
Zuotao Zhao^{128,129} 
Yuxiang Zhi¹³⁰ 
Torsten Zuberbier¹³¹ 
Ricardo D. Zwiener¹³²
Anthony Castaldo¹³³
- ¹Department of Dermatology and Allergy, Dermatological Allergology, Allergie-Centrum-Charité, Charité—Universitätsmedizin Berlin, Berlin, Germany
²Department of Dermatology, Medical University of Graz, Graz, Austria
³University of São Paulo, São Paulo, Brazil
⁴Microbiology Department, Faculty of Medicine, Kuwait University, Safat, Kuwait
⁵Allergy and Immunology Section, Department of Medicine, Hamad General Hospital, Doha, Qatar
⁶Department of Allergy and Immunology, Hospital Quiron Bizkaia, Bizkaia, Spain
⁷King Faisal Specialist Hospital & Research Center, Al Faisal University, Riyadh, Saudi Arabia
⁸Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil
⁹Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy
¹⁰Center for Children and Adolescents, University Hospital Frankfurt, Frankfurt, Germany
¹¹Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, USA
¹²Department of Dermatology, University Allergy Center, University Hospital Carl Gustav Carus, Technical University, Dresden, Germany
¹³Division of Allergy, Immunology and Dermatology, Department of Pediatrics, McGill University Health Center, Montreal, QC, Canada
¹⁴Instituto de Asma, Alergia y Enfermedades Respiratorias, Corrientes, Argentina
¹⁵Allergy Section, Division of Immunology, Department of Internal Medicine, Partner Bernstein Allergy Group, Partner Bernstein Clinical Research Center, University of Cincinnati, Cincinnati, OH, USA
¹⁶Division of Clinical Immunology and Allergy, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
¹⁷Department of Dermatology and Allergy Center, Odense University Hospital, Odense, Denmark
¹⁸Division of Allergy, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia
¹⁹Clinical Immunology/Internal Medicine Department, National Reference Center for Angioedema, Grenoble University Hospital, Grenoble, France
²⁰Department of Dermatology, Johannes Gutenberg University Mainz, Mainz, Germany
²¹HAE International (HAEi), Horsens, Denmark
²²Skåne University Hospital, Lund University, Lund, Sweden
²³Division of Clinical Immunology, Icahn School at Mount Sinai, New York, NY, USA
²⁴HAE Centre, Odense University Hospital, Odense, Denmark
²⁵Allergy Department, Hospital Universitario La Paz, IdiPaz, CIBERER U754, Madrid, Spain
²⁶Universidade Federal da Bahia, Salvador, Brazil
²⁷Serviço de Imunologia, Hospital das Clínicas Professor Edgard Santos, Salvador, Brazil
²⁸Department of Systems Medicine, University Hospital of Padua, Padua, Italy
²⁹School of Medicine, Universidad de Especialidades Espíritu Santo, Samborombón, Ecuador
³⁰RespiraLab, Research, Guayaquil, Ecuador
³¹Department of Vascular Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
³²Immunoallergy Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (CHLN), EPE, Lisbon, Portugal
³³Department of Medicine and Pediatrics, Penn State University, Hershey, PA, USA

- ³⁴Faculdade de Medicina do ABC, Santo André, Brazil
- ³⁵Alergoskin Alergia e Dermatologia SS Ltda, Santo André, Brazil
- ³⁶UCARE Center, São Paulo, Brazil
- ³⁷Faculdade de Medicina do ABC (FMABC), Santo André, Brazil
- ³⁸3rd Department of Internal Medicine, Hungarian Angioedema Reference Center, Semmelweis University, Budapest, Hungary
- ³⁹Department of Dermatology, Venereology and Allergology, University of Essen, Essen, Germany
- ⁴⁰Service de Dermatologie-allergologie, CHU Montpellier, Montpellier Cedex 5, France
- ⁴¹Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil
- ⁴²Department of Dermatology, Kayseri City Education and Research Hospital, Kayseri, Turkey
- ⁴³Private Practice, Lomas de Zamora, Argentina
- ⁴⁴Servicio de Alergia e Inmunología—Hospital Alende y Clínica Colón, Mar del Plata, Argentina
- ⁴⁵Ambulatorio di Dermatologia Allergologica e Professionale, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano (MI), Italy
- ⁴⁶The Dermatology Department of the Hospital de Bellvitge, Universitat de Barcelona, Barcelona, Spain
- ⁴⁷Unidad Alergia e Inmunología Clínica, Hospital Público Materno Infantil, Salta, Argentina
- ⁴⁸Center of Allergy and Immunology, City Clinical Hospital No. 52, Moscow Ministry of Healthcare, Moscow, Russian Federation
- ⁴⁹Department of Allergology and Clinical Immunology, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation
- ⁵⁰Division of Dermatology, Graduate School of Medicine, Kobe University, Kobe, Japan
- ⁵¹Division of Immunology and Allergic Diseases, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
- ⁵²Department of Dermatology, Hospital del Mar, IMIM, Universitat Autònoma, Barcelona, Spain
- ⁵³Department of Dermatology, D Y. Patil University School of Medicine, Mumbai, India
- ⁵⁴Department of Immunology, North Bristol NHS Trust, Southmead Hospital, Bristol, UK
- ⁵⁵Clinica de Dermatologia, Centro Hospitalar Universitário Coimbra, Coimbra, Portugal
- ⁵⁶Center of Allergy and Immunology, Tbilisi, Georgia
- ⁵⁷Marycliff Clinical Research, Spokane, WA, USA
- ⁵⁸Clinical Immunology, Medical School, University Center Health ABC, Santo Andre, Brazil
- ⁵⁹National School of Medicine, Instituto Politécnico Nacional, Mexico City, Mexico
- ⁶⁰Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
- ⁶¹NRC Institute of Immunology FMBA, Moscow, Russia
- ⁶²Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan
- ⁶³Department of Dermatology and Allergy, University Medical Center Giessen (UKGM), Justus-Liebig-University Giessen, Giessen, Germany
- ⁶⁴Instituto de Medicina Respiratoria—Rafaela, Santa Fe, Argentina
- ⁶⁵Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, Korea
- ⁶⁶Medical University of South Carolina, Charleston, SC, USA
- ⁶⁷European Center for Diagnosis and Treatment of Urticaria, Zabrze, Poland
- ⁶⁸Immunology & Allergy Unit, Department of Medicine, Campbelltown Hospital, Campbelltown, NSW, Australia
- ⁶⁹Division of Allergy & Clinical Immunology, Rappaport Faculty of Medicine, Bnai Zion Medical Center, Technion, Haifa, Israel
- ⁷⁰Clinic for Dermatology, Elbe Kliniken Buxtehude, Buxtehude, Germany
- ⁷¹Department of Dermatology, School of Medicine, Koç University, Koc, Turkey
- ⁷²Department of Dermatology, Venerology and Pediatric Dermatology, Medical University of Lublin, Lublin, Poland
- ⁷³Department of Dermatology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
- ⁷⁴Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
- ⁷⁵Clinica San Felipe, Lima, Peru
- ⁷⁶Department of Immunology, Addenbrookes Hospital Cambridge University NHS Foundation Trust, Cambridge, UK
- ⁷⁷UCLH, London, UK
- ⁷⁸Addenbrooke's Hospital Cambridge and University College Hospital, London, UK
- ⁷⁹Allergy/Immunology Division, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, TX, USA
- ⁸⁰Division of Immunology, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
- ⁸¹Allergy Unit "D. Kalogeromitros", 2nd Department of Dermatology and Venereology, University Hospital "Attikon", National and Kapodistrian University of Athens, Athens, Greece
- ⁸²Unidad de Alergia, Asma e Inmunología Clínica, Buenos Aires, Argentina
- ⁸³Department of Dermatology, The Urticaria Clinic, Salford Royal Foundation Trust, University of Manchester, Manchester, UK
- ⁸⁴Hemophilia Centre Rhine Main (HZRM), Moerfelden-Walldorf, Germany
- ⁸⁵Allergy and Clinical Immunology Department, Centro Médico Vitae, de Julio, Argentina
- ⁸⁶Department of Clinical Immunology and Allergology, Smolensk State Medical University, Smolensk, Russian Federation
- ⁸⁷Adult Immunology and Allergy Unit, Department of Medicine, Royal Hospital, Muscat, Oman

- ⁸⁸Klinik für Dermatologie, Universitätsklinikum Mannheim, Mannheim, Germany
- ⁸⁹Division of Dermatology, Kobe University Graduate School of Medicine, Kobe, Japan
- ⁹⁰Department of Internal Medicine, Saiyu Soka Hospital, Soka, Japan
- ⁹¹Department of Dermatology, Faculty of Medicine, Kırşehir Ahi Evran University, Kırşehir, Turkey
- ⁹²Allergy Unit, 2nd Pediatric Clinic, National and Kapodistrian University of Athens, Athens, Greece
- ⁹³Adults and Pediatrics Allergy Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
- ⁹⁴Department of Medicine, University of Cape Town, Cape Town, South Africa
- ⁹⁵Department of Dermatology and Allergology, Allergy Center Hessen, University Clinic Marburg, Marburg, Germany
- ⁹⁶University Hospital Sv. Ivan Rilski, Sofia, Bulgaria
- ⁹⁷Allergy Department, Hospital Universitario Severo Ochoa, Madrid, Spain
- ⁹⁸Instituto de Alergia e Inmunología del Sur, Buenos Aires, Argentina
- ⁹⁹Department of Dermatology, University of Rzeszow, Rzeszów, Poland
- ¹⁰⁰Angioedema Center, Barzilai Medical Center, Ashkelon, Israel
- ¹⁰¹Department of Medicine, University of California—San Diego, La Jolla, CA, USA
- ¹⁰²Departments of Medicine and Medical Oncology, University of Alberta, Edmonton, AB, Canada
- ¹⁰³Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands
- ¹⁰⁴London Allergy and Immunology Centre, London, UK
- ¹⁰⁵Dermatology Department, Marmara University School of Medicine, Pendik Research and Training Hospital, Istanbul, Turkey
- ¹⁰⁶Allergy and Clinical Immunology Department, Centro Medico Docente La Trinidad, Caracas, Venezuela
- ¹⁰⁷Allergy Unit, Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland
- ¹⁰⁸Hospital Santa Casa de Misericórdia de Vitória, Espírito Santo, Brazil
- ¹⁰⁹Dermatology Department, Hospital Sant Pau, Barcelona, Spain
- ¹¹⁰Department of Medicine, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia
- ¹¹¹Clinical Immunology and Allergy, Royal Adelaide Hospital, Adelaide, SA, Australia
- ¹¹²Service de Dermatologie et Allergologie, Hôpital Tenon, APHP, Sorbonne Université, Paris, France
- ¹¹³Department of Dermatology, University Medical Center, Mainz, Germany
- ¹¹⁴Department of Clinical Immunology, University Hospital Zurich, Zurich, Switzerland
- ¹¹⁵Department of Environmental Allergology, Jagiellonian University Medical College Kraków, HAE Center, University Hospital, Kraków, Poland
- ¹¹⁶Division of Allergy and Immunology, University of Toronto, Toronto, ON, Canada
- ¹¹⁷First Department of Dermatology and Venereology, National and Kapodistrian University of Athens, "A. Syggros" Hospital, Referral Center of Occupational Dermatological Diseases, Athens, Greece
- ¹¹⁸Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark
- ¹¹⁹Department of Dermatology, Venerology and Allergology and Leipzig Interdisciplinary Center of Allergology—Comprehensive Allergy Center, UMC Leipzig, Leipzig, Germany
- ¹²⁰Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
- ¹²¹Department of Dermatology, Erasmus MC, Rotterdam, The Netherlands
- ¹²²Clínica Privada Monte Grande, Buenos Aires, Argentina
- ¹²³Department of Dermatology, University of Erlangen, Erlangen, Germany
- ¹²⁴Dermatology Department of Sun Yat-sen Memorial Hospital, Guangzhou, China
- ¹²⁵Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea
- ¹²⁶Chair of Clinical Immunology and Rheumatology, Department of Psychodermatology, Medical University of Lodz, Lodz, Poland
- ¹²⁷Department of Biomedical and Clinical Sciences, Luigi Sacco Hospital, University of Milan, Milan, Italy
- ¹²⁸Department of Dermatology and Venereology, First Hospital, Peking University, Beijing, China
- ¹²⁹Beijing Key Laboratory of Molecular Diagnosis on Dermatoses, Beijing, China
- ¹³⁰Department of Allergy, Peking Union Medical College Hospital & Chinese Academy of Medical Sciences, Beijing, China
- ¹³¹Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité—Universitätsmedizin Berlin, Berlin, Germany
- ¹³²Servicio de Alergia e Inmunología, Hospital Universitario Austral, Buenos Aires, Argentina
- ¹³³HAE International (HAEi), Fairfax City, VA, USA

Correspondence

Marcus Maurer, Department of Dermatology and Allergy, Allergie-Centrum-Charité, Dermatological Allergology, Charité—Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany.
Email: marcus.maurer@charite.de

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ORCID

Marcus Maurer  <https://orcid.org/0000-0002-4121-481X>
Mona Al-Ahmad  <https://orcid.org/0000-0003-3720-7032>

Maryam Ali Al-Nesf  <https://orcid.org/0000-0001-9354-0214>
 Luisa Karla Arruda  <https://orcid.org/0000-0002-7505-210X>
 Riccardo Asero  <https://orcid.org/0000-0002-8277-1700>
 Jonathan A. Bernstein  <https://orcid.org/0000-0002-3476-1196>
 Mojca Bizjak  <https://orcid.org/0000-0003-2595-468X>
 Konrad Bork  <https://orcid.org/0000-0002-6084-4577>
 Laurence Bouillet  <https://orcid.org/0000-0001-8245-4767>
 Sigurd Broesby-Olsen  <https://orcid.org/0000-0002-1558-8471>
 Anette Bygum  <https://orcid.org/0000-0002-3004-0180>
 Ivan Cherrez-Ojeda  <https://orcid.org/0000-0002-1610-239X>
 Henriette Farkas  <https://orcid.org/0000-0003-2929-1721>
 Natalia L. Fili  <https://orcid.org/0000-0003-0327-3963>
 Atsushi Fukunaga  <https://orcid.org/0000-0003-2026-8154>
 Asli Gelincik  <https://orcid.org/0000-0002-3524-9952>
 Ana Giménez-Arnau  <https://orcid.org/0000-0001-9548-5423>
 Maia Gotua  <https://orcid.org/0000-0003-2497-4128>
 Hye-Ryun Kang  <https://orcid.org/0000-0002-2317-4201>
 Allen Kaplan  <https://orcid.org/0000-0002-6566-4743>
 Alicja Kasperska-Zajac  <https://orcid.org/0000-0002-2000-0070>
 Mitja Košnik  <https://orcid.org/0000-0002-4701-7374>
 Andrew MacGinnitie  <https://orcid.org/0000-0002-9451-3733>
 Martin Metz  <https://orcid.org/0000-0002-4070-9976>
 Iman Nasr  <https://orcid.org/0000-0003-0346-9675>
 Nikolaos G. Papadopoulos  <https://orcid.org/0000-0002-4448-3468>
 Wolfgang Pfützner  <https://orcid.org/0000-0002-8721-724X>
 Avner Reshef  <https://orcid.org/0000-0002-3324-7072>
 Marc A. Riedl  <https://orcid.org/0000-0003-3460-1544>
 Andaç Salman  <https://orcid.org/0000-0002-6407-926X>
 Mario Sanchez-Borges  <https://orcid.org/0000-0002-9308-6418>
 Peter Schmid-Grendelmeier  <https://orcid.org/0000-0003-3215-3370>
 Angèle Soria  <https://orcid.org/0000-0002-8726-6658>
 Gordon Sussman  <https://orcid.org/0000-0002-2202-2513>
 Anna Tagka  <https://orcid.org/0000-0003-3307-6522>

Simon Francis Thomsen  <https://orcid.org/0000-0002-4838-300X>
 Lilian Varga  <https://orcid.org/0000-0002-5484-364X>
 Daniel O. Vázquez  <https://orcid.org/0000-0001-9864-0783>
 Liangchun Wang  <https://orcid.org/0000-0002-5169-2751>
 Young-Min Ye  <https://orcid.org/0000-0002-7517-1715>
 Zuotao Zhao  <https://orcid.org/0000-0002-9595-6050>
 Yuxiang Zhi  <https://orcid.org/0000-0001-7539-6650>
 Torsten Zuberbier  <https://orcid.org/0000-0002-1466-8875>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Supplemental Material

What is GA²LEN?

GA²LEN, the Global Allergy and Asthma European Network, is a global consortium of leading clinical and research entities in the field of allergy and asthma. Its founding partners include the European Academy of Allergy and Clinical Immunology (EAACI) and the patients' organization representing European allergies and asthma patients (EFA). GA²LEN started under the European Union 6th Framework Program for Research, in 2004, with the mission to address the growing public health concern about allergic diseases. It has since expanded to include more than 90 leading European partners and collaborating centers and is one of the largest multidisciplinary networks of researchers in allergy and asthma worldwide. GA²LEN enhances the quality of research, translates research to new solutions, and communicates research findings with the ultimate objective of improving health care and quality of life for patients with allergies. It also aims to promote training and education in the field of allergology, for example with its GA²LEN Allergy Schools, Masterclasses, and Preceptorships[1].

Since its inception, GA²LEN has set up criteria for Centers of Excellence in Allergy. In 2015, an initiative to define, promote, and certify Centers of Reference and Excellence (COREs) for specific diseases was launched. Lead by the GA²LEN task force on urticaria[2], the Urticaria Centers of Reference and Excellence (UCARE) program was launched in 2016. It was the first implementation of the GA²LEN CORE initiative, embedded in the overall GA²LEN quality management system of allergy centers of excellence[3]. Currently, a worldwide network of 98 UCAREs in 36 countries is working on eight global research projects, e.g. CURE, the Chronic Urticaria Registry (www.urticaria-registry.com), UVERSICU (Urticarial vasculitis versus chronic spontaneous urticaria), and COLD-CE (Cold urticaria and other cold-induced reactions – Comprehensive Evaluation). The UCARE network hosts yearly annual global meetings (www.ucareistanbul2019.com; www.globalurticariaforum.org) as well as regional allergy schools and preceptorships (www.ga2len-ucare.com)[4].

What is HAEi?

HAE International (HAEi) is a nonprofit global umbrella organization that represents 83 hereditary angioedema (HAE) patient groups throughout the world. HAEi is dedicated to providing the motivation, expertise, and tools to help its member organizations firstly to broaden access to modern HAE medicines in countries where they are available, and secondly to make concerted and systematic efforts to take modern medicines to countries where there are none. HAEi delivers its

services through regional workshops and global conferences, expert medical advisors, and highly personalized interactions through its network of skilled and experienced Regional Patient Advocates (RPA).

Why do we need an Angioedema Center of Reference and Excellence (ACARE) program and network?

Angioedema is defined by transient and localized swelling, resulting from increased permeability of deep dermal/subcutaneous or mucosal/submucosal blood vessels. Angioedema, especially when recurrent, critically impairs patients' quality of life. Some forms of angioedema can lead to death by suffocation when the airways are affected and appropriate medicine is not administered in a timely fashion. Many patients suffer from delayed diagnosis of 10-20 years and are sometimes subject to mismanagement and unnecessary surgical procedures.

Angioedema is traditionally classified into mast cell/histamine-mediated or bradykinin-mediated (Table 1)[5-8]. The treatment of these two forms is very different[9]. The clinical presentation alone is insufficient to distinguish the mediator, but may give clues. A comprehensive and systematic history, clinical examination and blood evaluation and laboratory evaluation are essential for the identification of the cause of recurrent angioedema attacks and prescribing appropriate treatments[10].

The majority of recurrent angioedema cases are mast cell-mediated and occur either alone or in association with a typical skin rash, e.g. in patients with chronic spontaneous urticaria (CSU), NSAID intolerance or allergy. CSU is a common illness [11](1:100) and defined as the occurrence of itchy hives (wheals), angioedema, or both for at least 6 weeks. Autoimmunity and autoallergy are held to be the most common causes of CSU. Two out of three CSU patients suffer from recurrent angioedema, and the majority of these have associated hives. About 10-15% of CSU patients have solely recurrent angioedema (i.e. without hives) [8]. This type of CSU is sometimes also referred to as "idiopathic histaminergic acquired angioedema" (or "idiopathic non-histaminergic acquired angioedema" when high dose antihistamine treatment fails) (5). The quality of life in patients with CSU is markedly impaired, especially in those with recurrent angioedema. In patients with CSU, the family history is usually negative, and swellings are often located in the face, hands and feet, as well as genitalia. Angioedema of the upper airways may cause subjective breathing difficulties; however, suffocation does not occur in CSU. Some CSU patients with recurrent angioedema have mild or moderate recurrent abdominal discomfort, but visible abdominal swelling attacks with intestinal obstruction do not occur.

Epidemiologically, the most common reason of bradykinin-mediated angioedema is the intake of drugs that interfere with the degradation of bradykinin, for example angiotensin converting enzyme inhibitors. Although life threatening during attacks (oro-pharyngeal involvement), in most cases, but not all, the swellings stop after diagnosis and drug discontinuation, and no further treatment is needed. In contrast, HAE due to C1-inhibitor (C1-INH) deficiency (HAE-C1INH), is a rare, lifelong, and genetic (autosomal dominant) disease caused by mutations in the *SERPING1* gene[12]. The deficiency of C1-INH results in impaired inhibition of kallikrein, the central mediator of bradykinin generation. Virtually all HAE patients experience recurrent disabling swellings of the skin, and almost all have recurrent painful abdominal attacks, due to intestinal edema and ascites, which resemble acute abdomen and can last up to 5 days. Attacks affecting the upper airways occur in up to 50% of HAE patients, putting them at risk of death due to asphyxiation. The historical mortality rate before the advent of modern therapy is estimated at 30 percent[13]. Other types of HAE with unknown prevalence (due to mutations in *F12*, *PLG*, *ANGPT1* or *KNG1* genes), show normal levels of C1-INH (HAE-nC1INH). Nevertheless, these types are believed to also be mediated by bradykinin and the clinical pattern is very similar to HAE-C1-INH. Collectively, HAE can dramatically reduce a patient's quality of life, through significant impairments of psychological health, personal and family life, education, work productivity, and career advancement with constant fear of unpredictable attacks. An acquired form of C1INH deficiency is also known, which is associated with lymphoproliferative disorders and, less frequently, other malignancies or autoimmune or infectious diseases[14].

Regardless of the underlying mechanisms, patients perceive angioedema of the face and/or oral cavity as life-threatening, and their fear is often conveyed to the attending emergency medical staff [15]. Angioedema of the upper airways also results in fear of further attacks and suffocation. Many patients suffer for a decade or even longer before obtaining a correct diagnosis and are subject to pharmacological mismanagement and unnecessary surgical procedures. Providing patients with safe and efficacious medication and instruction on its use is a major goal for managing recurrent angioedema of all types. While on demand treatment ameliorates the symptoms of an individual attack, for most patients, having full control over their disease can only be achieved by effective preventive therapy.

Current guidelines recommend the use of patient-reported outcome measures (PROMs) to assess and monitor disease activity, impact, and control in patients with recurrent angioedema. Several PROMs are available for this[16, 17], including the Angioedema Activity Score (AAS)[18, 19], the Angioedema Quality of Life Questionnaire (AE-QoL)[20, 21] and the Angioedema Control Test (AECT)[22]. A satisfactory treatment response is one that reduces disease activity to levels of

mild or no disease, that normalizes quality of life, and that increases levels of disease control to well controlled or better. This is an important first step for a modern approach in which patients are completely free of recurrent angioedema symptoms.

Despite recent advances such as the global harmonization of angioedema classification and nomenclature [5, 6], the introduction of novel diagnostic tools and instruments[16], and the development of better treatment options[23-27], angioedema remains a challenging condition for many patients and their treating physicians. The global reality is that too many patients are not receiving the care and treatment they need. The delay in diagnosis and the rate of misdiagnosis remain unacceptably high[28, 29]. As a result, many patients are left to endure the impact of unpredictable, recurrent, painful and potentially fatal angioedema attacks and suffer from high rates of comorbidities including psychiatric and psychosomatic disease [30].

Centers of reference and excellence for specific diseases can help to improve the management of challenging conditions such as angioedema. In addition to serving as referral and second-opinion centers for difficult-to-treat patients, centers of reference and excellence will improve the understanding, management options, knowledge and awareness of diseases through research, clinical studies, education, and advocacy activities. Prominent examples of the benefit of centers of reference and excellence, beyond GA²LEN's UCAREs (Urticaria Centers of Reference and Excellence) and ADCAREs (Atopic Dermatitis Centers of Reference and Excellence), include the Centers of Excellence for Rare Diseases, and the European Competence Network on Mastocytosis [31].

The ACARE criteria

Infrastructure/setup

1. Hospital setting or affiliation - Center needs to be in a hospital or affiliated with a hospital with inpatient facilities to allow for extended diagnostic work up and management of exacerbation if needed.
2. Outpatient clinic with clinic hours for angioedema patients headed by expert - Center needs to have designated and expert leadership (experienced specialist physician) and to offer a minimum number of consultation hours per week for angioedema patients.

3. Care for children and adult patients - Center needs to provide care for angioedema patients of any age, either by center staff or affiliated specialists.
4. Team of dedicated staff, with specific angioedema training
5. Multidisciplinary approach - Center needs to interact with other specialties for the management of comorbidities, the treatment of patients with differential diagnoses, and to perform extended diagnostics.
6. Accessibility and visibility - Angioedema patients need to be able to find the center via information on the web; center needs to have referral network(s) of physicians; center needs to work with patient association(s), where applicable.
7. Communication skills - Center staff needs to be able to communicate adequately with angioedema patients in national language and in English.
8. Quality management - Center needs to have a quality management system in place, needs to have written protocols and standard operating procedures.
9. Structured documentation, record keeping and archiving of patient data
10. Critical incidence reporting and error management
11. Assessment of patient satisfaction and unmet needs - Center needs to regularly assess how satisfied patients are with the work of the center and take appropriate action based on the outcome.
12. In team communication - Center needs to have regular meetings to discuss patients, projects and concepts. Decisions should be protocolled and followed by action where applicable.
13. Active recruitment of research funding and support for educational activities and advocacy on angioedema
14. Support of the ACARE network
15. "Never give up" attitude

Management of angioedema

16. Knowledge of and adherence to international angioedema guidelines and consensus documents
17. Knowledge and use of current consensus nomenclature and classification of angioedema
18. Knowledge and use of guided history taking/anamnesis
19. Knowledge and use of differential diagnostic algorithm
20. Knowledge and use of standardized assessments and monitoring of disease activity, impact and control

21. Identification of comorbidities and underlying causes - Center needs to have access to and use measures to identify comorbidities and causes of chronic recurrent angioedema, for example C1 inhibitor testing and genetic testing
22. Family screening and pedigree charting
23. Knowledge of therapeutic options and their use for improving patient quality of life
24. Counseling -Counseling of patients and their families, for example on triggers of exacerbation, on emergency medication/measures, daily life issues can help to optimize angioedema management.

Clinical and Basic Research

25. Scientific orientation - Center staff needs to be up-to-date with the literature on angioedema, especially on pathogenesis, for example by participation in journal club, attending annual meetings of scientific societies, membership in scientific societies.
26. Scientific activity - Angioedema research activities in basic science, clinical science, translational science, epidemiology, and/or public health
27. Scientific productivity - Center needs to show that its research activities result in publications and other scientific output.
28. Clinical trials - Center needs to participate in clinical trials, pharma- and/or investigator-initiated; diagnostic and/or therapeutic trials on angioedema
29. Participation in registry

Education

30. Educational activities

Advocacy

31. Increase awareness of angioedema including HAE
32. Interaction with and support of HAEi and national angioedema patient organization(s)

Accreditation process

GA²LEN and HAEi encourage all angioedema centers to consider to become ACAREs and be part of the GA²LEN/HAEi ACARE network. Angioedema specialty centers worldwide can apply to become an ACARE by contacting the ACARE office (acare@ga2len.net, www.acare-network.com). In their application (application form is available for download at www.acare-network.com), centers should describe their motivation to become an ACARE and confirm that they

are ready to fulfill the requirements, as outlined by the checklist provided (Fig. 1). The ACARE office will review the application and schedule an audit visit. Applicant angioedema centers that are located at member institutions of the UCARE network are eligible for privileged access to the ACARE network. Their ACARE accreditation audit will be done with the next scheduled UCARE audit. Generally, all 32 ACARE requirements have to be met. If it becomes clear during the audit, that certain requirements are not (yet) fulfilled, GA²LEN is committed to provide support to help the center address these shortcomings and achieve ACARE status. Upon successful audit, GA²LEN and HAEi award a two-year certificate (Fig. 1b) that can be renewed upon successful re-audit. If the first re-audit is successful, the certificate is extended for three years. Each subsequent successful re-audit leads to four additional years of accreditation. Recertification of ACARES requires their active participation in ACARE projects, meetings and activities.

The ACARE network is peer-reviewed, therefore certified ACAREs will become members of the ACARE network, and their head and deputy head(s) join the ACARE audit team. Certified ACAREs enjoy the benefits of being a member of the ACARE network (i.e. participation in network of excellence activities, multicenter projects, etc.). They are expected to participate in ACARE meetings and to contribute to ACARE projects. No financial obligations to GA²LEN or HAEi result from becoming or being an ACARE.

The audit and certification process

The audit and re-audit process involves an on-site visit by at least one member of the GA²LEN/HAEi ACARE audit team. The ACARE audit team consists of all heads and deputy heads of certified ACAREs. A representative from HAEi may also participate as an observer. During this audit visit, the center presents its facilities and team to the auditor(s), according to the audit checklist (Fig. 1). The audit visit is concluded by a collegial assessment and information by the auditor on the results of the audit. Shortcomings, if identified, will be discussed, and strategies to overcome them are jointly developed with the spirit of achieving the common goals of the ACARE network. An audit report will be provided by the auditor, to the ACARE office. The ACARE office will inform all members of the ACARE steering committee of the audit outcome and the recommendation of the auditor(s). The applicant team will receive a written audit report and the GA²LEN/HAEi ACARE certificate if certified (Fig. 2). In case certain provisions are missing, the audit report will contain specific recommendations and timelines to address this. GA²LEN is obligated to help centers to achieve ACARE status.

HAEi member organizations and regional patient advocates

HAEi currently represents patient organizations in 83 countries (www.haei.org), and delivers its services through 7 Regional Patient Advocates (RPA) that cover 8 regions of the world including: 1) Central and Eastern Europe, 2) Gulf Region & Middle East, 3) Asia Pacific, 4) South America & Mexico, 5) Sub-Sahara Africa, 6) Central America & Caribbean, 7) South Eastern Europe, 8) Mediterranean & Maghreb countries. The GA²LEN/HAEi ACARE initiative aims to establish ACARE throughout the 8 HAEi regions as well as in North America and Northern and Western Europe, which are not covered by the RPA program.

Governance and funding

The GA²LEN/HAEi ACARE network will set up a steering committee that reflects the diversity of a global organization. The ACARE steering committee will work closely with HAEi's leadership and RPAs to jointly sponsor and implement patient/physician educational programs along with initiatives to raise awareness and advocate for accurate diagnosis and access to modern angioedema medicines. The ACARE office helps the network to coordinate applications, audits, re-audits, meetings and projects. GA²LEN and HAEi support the ACARE office and network, financially and logistically, and the ACARE network aims to recruit funding from sources outside of GA²LEN and HAEi for its projects and meetings.

Interaction with other GA²LEN networks of centers of reference and excellence

The ACARE network will seek interaction with other GA²LEN networks, especially with its twin network for urticaria, the UCARE network. Joint activities and meetings of the ACARE and UCARE networks will be coordinated by GA²LEN. Angioedema is a common feature of chronic urticaria, and the UCARE network aims to improve the management and the understanding of angioedema linked to chronic urticaria. UCAREs are encouraged to extend their attention, expertise and activities on angioedema to bradykinin-mediated forms and should consider to become ACAREs. ACAREs are encouraged to extend their interest, proficiency and efforts to urticaria beyond angioedema and should consider to become UCAREs.

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