Definition, acronyms, nomenclature, and classification of angioedema (DANCE): AAAAI, ACAAI, ACARE, and APAAACI DANCE consensus

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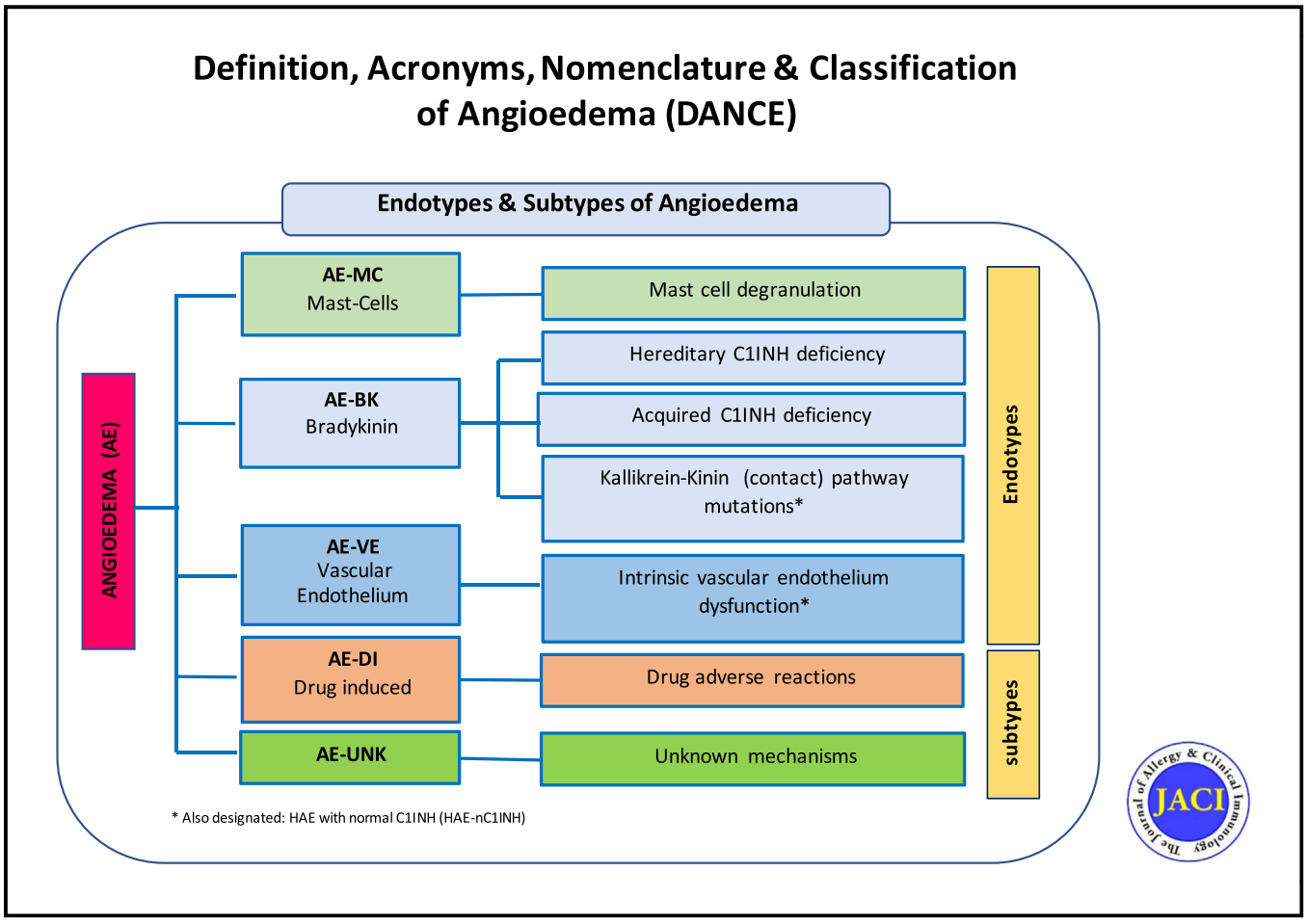
GRAPHICAL ABSTRACT



Capsule summary: Angioedema syndromes are clinically heterogeneous, hereditary, or acquired and are caused by different pathogenetic mechanisms. Results of a global expert consensus on the classification and terminology of various angioedema types and endotypes are presented.

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Background: Angioedema (AE) manifests with intermittent, localized, self-limiting swelling of the subcutaneous and/or submucosal tissue. AE is heterogeneous, can be hereditary or acquired, may occur only once or be recurrent, may exhibit wheals or not, and may be due to mast cell mediators, bradykinin, or other mechanisms. Several different taxonomic systems are currently used, making it difficult to compare the results of studies, develop multicenter collaboration, and harmonize AE treatment.

Objective: We developed a consensus on the definition, acronyms, nomenclature, and classification of AE (DANCE).

Methods: The initiative involved 91 experts from 35 countries and was endorsed by 53 scientific and medical societies, and patient organizations. A consensus was reached by online discussion and voting using the Delphi process over a period of 16 months (June 2021 to November 2022).

Results: The DANCE initiative resulted in an international consensus on the definition, classification, and terminology of AE. The new consensus classification features 5 types and endotypes of AE and a harmonized vocabulary of abbreviations/acronyms.

Conclusion: The DANCE classification complements current clinical guidelines and expert consensus recommendations on the diagnostic assessment and treatment of AE. DANCE does not replace current clinical guidelines, and expert consensus algorithms and should not be misconstrued in a way that affects reimbursement of medicines prescribed by physicians using sound clinical judgment. We anticipate that this new AE taxonomy and nomenclature will harmonize and facilitate AE research and clinical studies, thereby improving patient care. (J Allergy Clin Immunol 2024;■■■:■■■-■■■.)

Key words: *Angioedema, acronyms, classification, terminology, types*

Angioedema (AE) is defined as "intermittent, localized, and self-limiting swelling of the subcutaneous and/or submucosal tissue, due to a temporary increase in vascular permeability."[1,2] The pathophysiologic abnormalities in AE are attributed to mechanisms controlling endothelial barrier function, which normally maintain the stability of capillaries and small venules.[3] In AE, dysregulated endothelial permeability leads to excess plasma leakage from the blood vessels into the surrounding tissues, resulting in transient swelling.[3] AE manifests with recurrent, reversible swelling episodes of skin and subcutaneous tissues or

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submucosal surfaces. Involvement of the upper airway is life-threatening, and intestinal wall swelling may result in obstruction and ascites.[4,5]

Most recurrent AE episodes are driven by mast cell (MC) mediators, as in urticaria (URT), a disease defined by the international guideline for URT as the occurrence of wheals, AE, or both.[6] In chronic spontaneous URT (CSU), most patients report recurrent wheals (hives), often with concomitant AE, but in ~10%, AE occurs without wheals.[6,7]

Hereditary AE (HAE) due to C1 inhibitor *(C1INH)* deficiency is a rare genetic disorder resulting from low levels or dysfunctional *C1INH,* the primary role of which is to control blood vessel permeability.[8] HAE due to *C1INH* deficiency was first described by Donaldson and Evans,[9] followed by a series of clinical cases by Landerman.[10] Over the last 57 years, more than 850 different *C1INH* gene *(SERPING1)* mutations have been documented, located on chromosome 11.[11-13] Misdiagnosis of intestinal swelling may lead to unnecessary abdominal surgery,[5] and attacks involving the oropharyngeal–lingual region, if not promptly recognized and treated, may cause death due to asphyxiation.[14,15] As a lifetime chronic illness, HAE severely affects all aspects of daily activities and health-related quality of life, and it considerably burdens health care systems.[16-19] International guidelines regarding the diagnosis and management of HAE have been published and regularly updated.[20-22]

Recent evidence shows that the mechanisms underlying AEs are heterogeneous and complex. Examples include the disinhibition of the kallikrein/kinin system (KKS), leading to local and transient excess production of bradykinin (BK), as in hereditary or acquired types of *C1INH* deficiency, reduced catabolism of BK (ie, drug induced), and intrinsic abnormalities in elements of the vascular endothelium.

In the last 2 decades, several new HAE syndromes were described, all with normal quantity and activity of *C1INH* cosegregating with different gene mutations.[23-29] In view of the aforementioned new evidence, the conventional paradigm of AE classification needs to be reevaluated.[30]

Previous classifications of AE

Several attempts to classify AE have been made in the past. An extensive literature search in 2016 found 25 international consensus statements on the definition and classification of AE published over the previous 13 years.[31] The pivotal consensus statement by Cicardi et al[1] provided an extensive evidence-based foundation for all forms of AE known at that time, including incidence, clinical presentation, pathogenesis, diagnosis, and treatment. Subsequent consensus statements, guidelines, and practice parameters provided updated and revised classifications of AE.[20-22]

Rationale for updated classification and terminology of AE

Currently, AE terminology and abbreviations/acronyms in the medical literature differ by country, professional organizations, and authors. Consequently, dissimilar wording and terminology has led to confusion and inconsistencies.[31] The Hereditary Angioedema Working International Group (HAWK) consensus was the first to formulate an AE-specific vocabulary of acronyms and taxonomy.[1] However, the diverse vocabulary used in publications motivated a call for unified terminology.[32-34]

The current AE classification system leaves many taxonomical gaps. The finding of novel mutations causing HAE led to the general term "HAE with normal C1 inhibitor," based on the presence or absence of *C1INH* during a preliminary assessment. Also, MC-mediated AEs (ie, CSU) are separately classified, and other common AEs are not yet listed by any classification system.[6] In addition, AE due to drugs (ie, angiotensin-converting enzyme [ACE] inhibitors) and rare AE diseases caused by vascular hyperpermeability are also not included.

These shortcomings call for an updated, comprehensive, and widely accepted classification system, one that combines clinical expression, mechanisms, biomarkers, and genetics, and that can reflect all the different AE types. Such a classification system will harmonize publications' vocabulary and improve patient care by avoiding misdiagnosis and assisting in tailoring targeted therapies.

The definition, acronyms, nomenclature, and classification of AE (DANCE) initiative addresses this unmet need and provides a global consensus on the definition and classification of AE and its nomenclature, including abbreviations/acronyms, covering all AE types and subtypes.

METHODS

Literature search

On June 22, 2021, two independent reviewers (T.B. and C.V.) separately conducted a systematic PubMed literature search of the last 10 years with the MeSH terms "angioedema AND definition" (76 results) and "angioedema AND classification" (178 results), in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines.[35] All studies were published in German, English, or Spanish. Additionally, we included and manually checked references in key publications on AE because definitions and classifications of AE are often only reported as part of the patient or study description in the full text.

The studies had to report a definition and/or classification of AE to be eligible. On the basis of these predefined criteria, the reviewers screened all study titles and abstracts for suitability and subsequently reviewed suitable articles in full text to evaluate their eligibility. Finally, 44 publications were included and analyzed.

The following details were extracted from each study: first author's name and year of publication; definition of AE; classification of AE; and names and abbreviations of AE types and subtypes. This information was made available to the DANCE steering committee and expert panel members.

DANCE steering committee and expert panel

The DANCE steering committee consisted of 13 AE experts, diverse in both professional background (8 clinical immunologists/allergists, 3 dermatologists, 1 pediatrician) and geography (Brazil, Canada, China, Germany, Hungary, India, Israel, Japan, New Zealand, South Africa, Spain, United States). The steering committee was led by Avner Reshef (Israel), Markus Magerl (Germany), and Marcus Maurer (Germany).

The DANCE expert panel initially recruited 97 experts. Five experts did not respond in round 1, and 1 did not respond in round 3. Consequently, 91 experts from 35 countries, including the

steering committee members, contributed to the consensus. They came from different fields of expertise, including dermatology, allergy, immunology, pediatrics, otolaryngology, gastroenterology, and emergency medicine, as delegates of 53 medical societies (see Table E1 in the Online Repository available at www.jacionline.org). Participation in the expert panel was facilitated by publicized calls and a registration platform on the Angioedema Centers of Reference and Excellence (ACARE) website to represent interdisciplinary and intercontinental views on AE and to gain a robust consensus (acare-network.com/projects/#past). All expert panel members confirmed that they are actively treating patients with AE and/or were involved in research directly related to AE, and that they had obtained a mandate to be the delegate of a national or international scientific or medical society; they further confirmed in writing their nomination of experts as delegates, endorsement of the outcome of this project, and support of its dissemination. No honoraria were paid for participation.

Development of rationale and concept of DANCE

On the basis of the literature search results, the steering committee leaders developed the rationale and general concept for the DANCE initiative. The first draft set of statements was presented to the steering committee in video conferences in September and October 2021. After the group had agreed on the scope of the initiative and the rationale and principles of the new classification, the steering committee leaders continued to refine the definition of AE, names assigned to the different types and subtypes of AE, abbreviations/acronyms, and classification. After further discussion, 18 statements on the nomenclature and classification of AE were proposed and presented to the panel members for the first round of voting, using a Delphi process (Fig 1). The proposed nomenclature reflected the current International Classification of Diseases and Related Health Problems (ICD) and the therapeutic indications and target diseases used in the summaries of product specifics of current treatments for AE.

Establishment of consensus by Delphi process

The global expert panel established the core consensus via a Delphi process over a period of 8 months (March 14 to November 15, 2022). The Delphi process is a validated approach to evaluate and refine group opinions *(vox populi)* by iterative rounds of questioning without the influence of group pressure or dominant individuals.[36] The process enables a free exchange of views while ensuring that all opinions are equally considered.[36-38] The DANCE Delphi process consisted of 3 rounds of voting, handled by Thomas Buttgereit, a trained Delphi facilitator. A dedicated online polling system (Welphi, Decisioneyes, Lisbon, Portugal) was used, similar to a previous Delphi process on HAE treatment goals.[39]

In round 1 (49 days, from March 14 to May 1, 2022, with 92 respondents) of the DANCE Delphi process, free-text responses of the expert panel members to the suggestions of the steering committee for the definition, nomenclature, and classification for AE were collected, together with the evaluation of each suggestion by use of a 5-point Likert scale (0 = completely disagree, 1 = mostly disagree, 2 = undecided, 3 = mostly agree, 4 = completely agree). Respondents were asked to consider their clinical experience, their patient management protocols, and their broader knowledge. Consensus was defined *a priori* as agreement (mostly agree or completely agree) by at least 75% of respondents. Percentage agreement and all comments were recorded for each statement.[38] The Delphi facilitator provided an anonymized summary of the outcomes and presented the results to the panel members. The steering committee developed a revised version of the statements that was based on the results and feedback obtained in round 1.

In round 2 (from July 21 to August 14, 2022), expert panel members were asked if they agreed or disagreed with the revised statements. After round 2, consensus was reached on the definition of AE and 15 of 18 additional statements, and the outcomes were again summarized and presented to the expert panel members. For the third and final round (from October 25 to November 15, 2022), the steering committee developed revised versions of the 3 statements for which consensus was not achieved in round 2. These revised statements considered the feedback of panel members who did not agree during round 2, with additional information, evidence, and context wording. The third Delphi round established consensus on all revised statements (Fig 1 and Table I).

RESULTS

Definition of AE and related terms

The present DANCE consensus provides 3 AE-related definitions (Table I, statements 1-3). The consensus definition of AE is "a paroxysmal, localized, and self-limiting swelling of the subcutaneous and/or submucosal tissue, due to a temporary increase in vascular permeability."[1] This definition highlights the 3 key features of manifestations of AE. The panel preferred "paroxysmal" to "intermittent" to emphasize the acute nature of AE attacks. Because swelling can simultaneously affect subcutaneous and submucosal tissues, the wording "and/or" was chosen. The DANCE expert panel chose not to include "potentially life-threatening" because death from asphyxiation is rare and does not occur in all types of AE.

The second definition (Table I, statement 2) relates to wheals (hives). These welts occur mainly in URT and are characterized by 3 typical features: a sharply circumscribed superficial central swelling of variable size and shape, almost invariably surrounded by reflex erythema; an itching or sometimes burning sensation; and its fleeting nature, with the skin returning to its normal appearance, usually within 30 minutes to 24 hours, as defined by a multidisciplinary guideline.[6] In a recent systematic review, two-thirds of patients with CSU were reported to have concomitant AE in one study, and the pooled prevalence of AE across all CSU studies analyzed was 36.5%.[40] Some experts thought this definition should not emphasize the evanescent nature of the wheals because they can persist for several days. Patients with wheals that last longer than 24 hours should be assessed for other diseases, including urticarial vasculitis.

Our third definition (Table I, statement 3) relates to AE prodromes. These signs or symptoms (1) predate and often indicate the onset of an AE attack, (2) manifest subjectively (ie, pain, tingling, anxiety) or objectively (ie, skin rash, flushing, diarrhea), (3) typically occur 1 to 12 hours before the onset of an AE attack, and (4) may recur in the same manner, allowing patients to predict an impending attack.[41] This definition is based on many observations, clinical studies, and publications on prodromes as predictors of AE attacks in patients with HAE.[41,42] Some experts commented that there is a need for a clearer demarcation of the

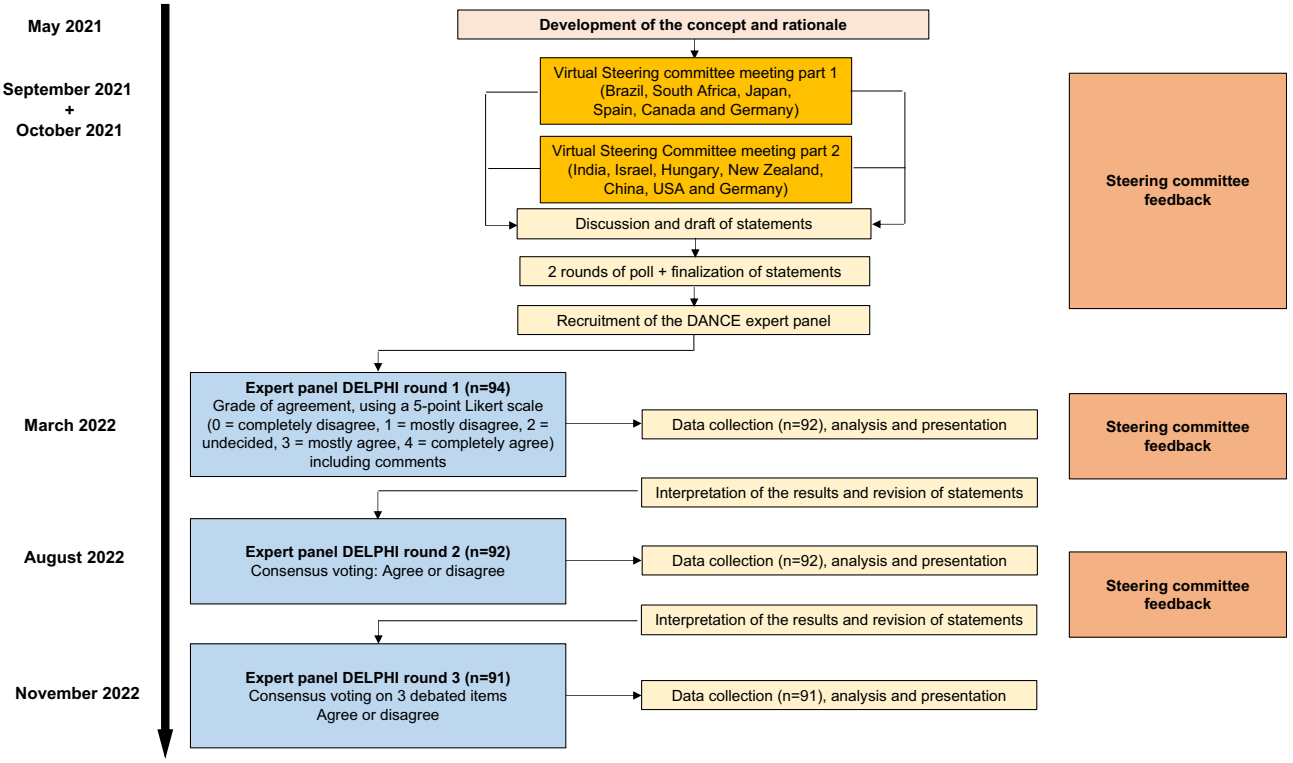

FIG 1. Timeline of the Delphi process (May 2021 to November 2022). Experts from 35 countries, including steering committee members, representing 53 medical societies, contributed to the consensus. More information is provided in Tables E5 and E6 in the Online Repository available at www.jacionline.org.

time course between prodromes and attacks regarding location and clinical features. Nonetheless, recent studies show that HAE patients can distinguish prodromes from attacks, and prodromes can foretell subsequent attack location and intensity.[41] Because prodromes are not necessarily followed by an attack, the words "often" and "possible" were introduced to indicate that prodromes are not always followed by an AE attack.

Nomenclature of AE

The DANCE initiative recommends using "AE" as the abbreviation for all types of AE (Table I, statement 4). This standard, etymology-driven, and short term uses the first letters of the 2 components of the word "angioedema." However "AE" also serves to abbreviate other terms, including "adverse events" in clinical trials. When used in publications, its introduction at first use and application in reference to angioedema will minimize confusion. Some experts suggested including an abbreviation for chronic or recurrent AE. However, the minimum number of attacks, or time during which swellings occur in recurrent or chronic AE, is not well defined and requires further research.

The DANCE expert panel further recommends that abbreviations/acronyms for inherited AE types start with the letter H, for hereditary (ie, HAE), and that the letter A, for acquired, is reserved for the abbreviation of AE due to acquired C1 inhibitor deficiency, traditionally abbreviated AAE (Table I, statement 5). Most cases and types of AE are acquired rather than hereditary; therefore, "acquired" is not needed for the names of nonhereditary subtypes of AE. The exception to this rule is AE due to acquired *C1INH* deficiency (AAE-C1INH). As a result of the wide overlap between different etiologies of acquired *C1INH* deficiency, DANCE's classification follows the previous classification consensus and does not divide AE-C1INH into subcategories.[1]

Abbreviations/acronyms of AE subtypes are recommended to start with the disease first (ie, HAE, AAE, AE), followed by a dash/hyphen and mechanism or biomarker (Table I, statement 6). This approach differs from previous ones, including the 2014 HAWK group nomenclature.[1] The panel agreed that starting the designation of AE subtypes with the clinical presentation (phenotype) provides the most crucial information first and whether it is hereditary or acquired. Indication of the underlying pathomechanism or the associated biomarker then follows. This will simplify abbreviations of AE subtypes (Table I, statement 7).

Two forms of HAE due to *C1INH* deficiency are described: HAE due to *C1INH* quantitative deficiency (characterized by low antigenic and functional *C1INH* levels) and HAE due to *C1INH* dysfunction (characterized by normal or elevated antigenic but low functional *C1INH* levels). These subtypes are traditionally referred to as type 1 and type 2, respectively. Thus, the panel recommends that they be abbreviated HAE-C1INH-Type1 and HAE-C1INH-Type2, respectively (Table I, statement 8). This intends to preserve this established HAE terminology and align it with recent practice parameters.[20-22]

In addition, the abbreviations of coagulation-contact system components proposed by Schmaier et al[43] were adopted (Tables I and II, statement 9). This publication, authored by 11 distinguished hematology experts, was approved by the International Society on Thrombosis and Hemostasis.[43] The authors recommended that the new abbreviations be utilized in all future communications and publications in the field.

TABLE I. Summary of key statements and rate of agreement obtained after 3 rounds of Delphi process

Statement no.	Statement	Agreement*
1	Angioedema is defined as "a paroxysmal, localized, and self-limiting swelling of the subcutaneous and/or submucosal tissue, due to a temporary increase in vascular permeability" (modified from Cicardi et al,[1] Allergy 2014).	98%
2	Wheal in urticaria is characterized by 3 typical features (modified from Zuberbier et al,[6] Allergy 2022): 1. Sharply circumscribed superficial central swelling of variable size and shape, almost invariably surrounded by reflex erythema. 2. Itching or sometimes burning sensation. 3. Fleeting nature, with skin returning to normal appearance, usually within 30 minutes to 24 hours.	99%
3	Prodromes of AE are characterized by (modified from Leibovich-Nassi and Reshef,[41] Clin Rev Allergy Immunol 2021): 1. Sign or symptom often indicating impending onset of attack. 2. Manifested subjectively (ie, pain, tingling, anxiety) or objectively (ie, skin rash, flushing, diarrhea). 3. Typically occur 1 to 12 hours before attack. 4. May reiterate in the same manner, allowing patients to predict possible onset of upcoming attacks.	97%
4	The collective acronym for all types of angioedema will be AE (plural, AEs).	100%
5	Acronyms for inherited angioedema (AE) types will start with letter H, for hereditary (ie, HAE-C1INH); and use of letter A, for acquired, before AE is reserved for AE due to acquired *C1INH* deficiency (ie, AAE-C1INH).	99%
6	Acronyms will assemble by using disease first (ie, HAE), followed by mechanism/biomarker, which may be separated by dash or hyphen (ie, HAE-FXII, AE-ACEI).	99%
7	Mechanisms, mediators, or biomarkers will be inscribed without dash or hyphen (ie, ACEI, C1INH).	95%
8	The 2 known types of HAE due to *C1INH* deficiency will use suffix Type1 or Type2 (ie, HAE-C1INH-Type1, HAE-C1INH-Type2).	99%
9	Acronyms of all coagulation-contact system components will follow definitions of Schmaier et al[43] (J Thromb Haemost 2019).	99%
10	Acronyms currently used to describe AE treatment strategies will remain the same (ie, ODT, STP, LTP).	99%
11	AE categories will be assembled into 3 endotypes and 2 subgroups.	89%
12	All recurrent mast cell–mediated AEs (histamine mediated, "allergic anaphylactic") will be designated as AE-MC endotype.	99%
13	All AEs related to pathomechanism of the contact kallikrein/kinin system (KKS) will be designated as AE-BK endotype.	98%
14	All AEs related to intrinsic vascular endothelium abnormalities and mutations will be designated as AE-VE endotype.	97%
15	HAE-HS (HS3ST6 mutation) is categorized as AE-VE endotype.	98%
16	All drug-induced AEs without proven pathomechanisms will be designated as AE-DI type.	85%
17	ACE inhibitor–induced AE is categorized as AE-DI type.	93%
18	AEs with still-unknown mechanism/triggers will be designated as AE-UNK type.	90%
19	Episodic AE with eosinophilia (EAE, Gleich syndrome) is categorized as AE-UNK type.	100%

FXII, Factor XII; *LTP,* long-term prophylaxis; *ODT,* on-demand treatment; *STP,* short-term prophylaxis.
*Rate of agreement reflects percentage of experts who agreed with the statement, as determined during 3 Delphi rounds of consensus finding.

The DANCE experts propose that the abbreviations currently used to describe AE treatment strategies remain the same—that is, ODT, STP, and LTP for on-demand treatment, short-term prophylaxis, and long-term prophylaxis, respectively (Table I, statement 10). These terms and their abbreviations already have their place in the AE literature, clinical trials, and practice parameters and are well established in HAE treatment plans.

Classification of AE

AE subtypes will be assigned to 5 different types, the first 3 of which designate AE endotypes (Table I, statement 11, Fig 2). The DANCE classification is meant to complement current guidelines and other consensus algorithms for the diagnosis and treatment of AE patients. It aims to improve the characterization of AE subtypes so that ongoing efforts to investigate mechanisms of these poorly understood conditions will lead to more meaningful and generalizable results.[20-22] The DANCE classification of AE uses all the currently available data to formulate terms that reflect phenotypic expressions, genetics, mechanisms, and biomarkers but acknowledges that specific biomarkers are still lacking for many conditions, so changes may be needed as new evidence emerges. Any of the proposed categorizations may change as more evidence becomes available. It is important to emphasize that the DANCE classification and its future updates should not be misconstrued in a way that would affect reimbursement of physician-prescribed medications for HAE variants.

TABLE II. Abbreviations/acronyms of coagulation-contact system components

Name	Acronym
Bradykinin	BK
Cleaved high-molecular-weight kininogen	cHK
Activated factor XII	FXIIa
Coagulation factor XII (Hageman factor)	FXII
Coagulation factor XI (Rosenthal factor)	FXI
High-molecular-weight kininogen (Williams/Fitzgerald factor)	HK
Low-molecular-weight kininogen	LK
Plasma prekallikrein (Fletcher factor)	PK
Plasma kallikrein	PKa

Modified from Schmaier et al[43] (J Thromb Haemost 2019).

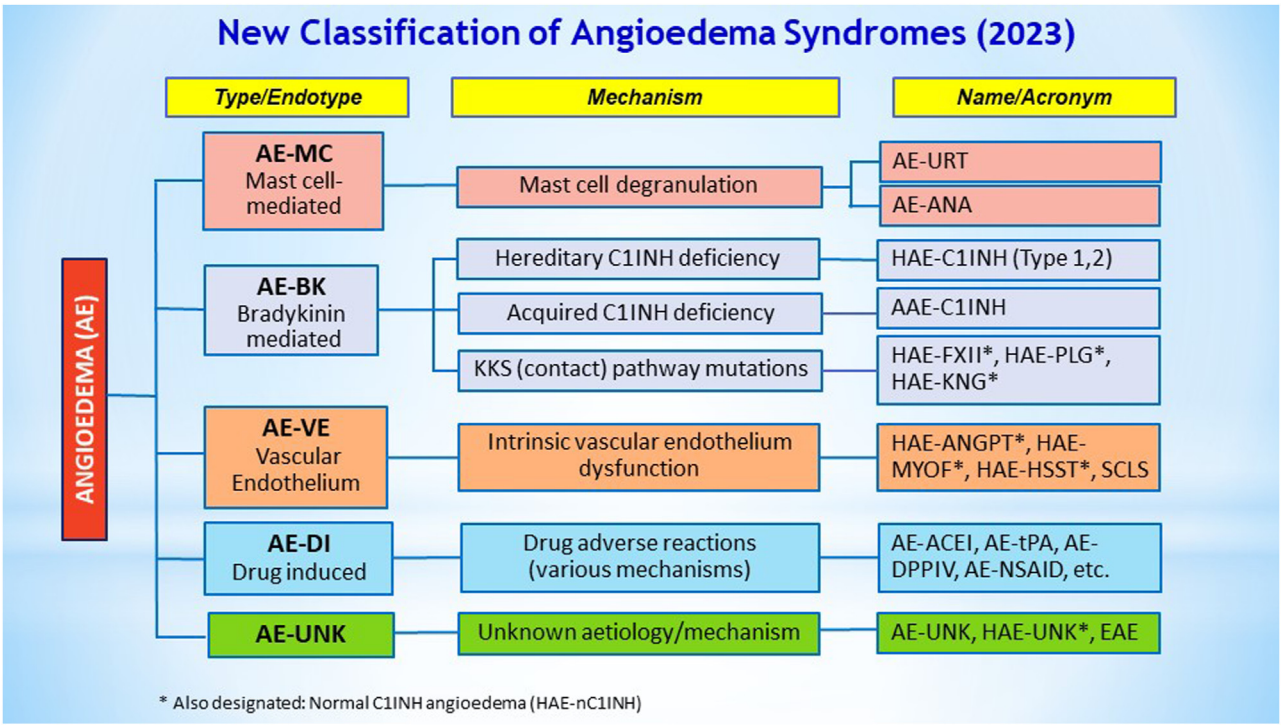

FIG 2. Proposed new classification of all AE entities according to clinical expression, currently available information on pathomechanisms, and known pathogenesis. Five types/endotypes are listed by their putative mechanisms and new terminology (abbreviation/acronym).

MC-mediated AE

Mast cell–mediated AE (AE-MC) replaces "histamine-mediated AE," "allergic," or "anaphylactic"; and will be considered an endotype (Table I, statement 12). This change is based on the understanding that MCs secrete many proinflammatory products beyond histamine.[44] Thus, this endotype is based on a cell rather than a mediator, and recurrent AE-MC (ie, CSU) often does not respond to higher-than-standard doses of antihistamines, although it often does respond to omalizumab. Subtypes of AE-MC include acute URT, inducible URT, and CSU, with up to 70% of patients developing AE.[6,7] AE-MC also comprises AE in the context of anaphylaxis because it often manifests with AE attacks at various organs and carries the risk of asphyxiation if involving the oropharyngeal area.[45]

BK-mediated AE

The AE-BK endotype comprises all BK-mediated subtypes of AE (Table I, statement 12), including all AEs attributed to the KKS cascade and BK production.[8] Of note, all types of AE attributed to the activation of the KKS are held to be BK driven, but BK may be generated by KKS-independent mechanisms in some types of AE—for example, in HAE-PLG—by a mutant plasmin (plasmin-Glu^{311}).[46] In addition to including HAE-C1INH and AAE-C1INH, which are both associated with *C1INH* deficiency, this category will comprise 3 recently identified genetic variants, namely HAE-FXII, HAE-PLG, and HAE-KNG, as well as HAE-UNK (unknown).

The DANCE classification distinguishes between hereditary and acquired AE, which comprise the known conditions caused by *C1INH* deficiency. All types of HAE that are not caused by *C1INH* deficiency are clinically categorized as HAE-nC1INH (Fig 3), with further subcategorization by the genetic or molecular cause—for example, HAE-nC1INH due to factor XII (FXII) mutation.

AE due to intrinsic vascular endothelium dysfunction

This new category refers to intrinsic vascular endothelium dysfunction as an endotype (Table I, statement 14). The decision to form a new category within this updated classification is based on new evidence on the central role of the vascular endothelium in the pathologic processes leading to AE attacks. This endotype will include 3 of the newly described mutations—HAE-ANGPT, HAE-MYOF, and HAE-HSST (Table III)—and HAE-UNK, as well as systemic capillary leak syndrome (SCLS, also known as Clarkson disease).

Although there is little information on the underlying pathogenesis of HAE due to heparan sulfate 3-*O*-sulfotransferase 6 mutation (HAE-HSST), with only one family reported,[29] the disease-driving mutation affects heparin sulfate (HS)-glucosamine 3-*O*-sulfotransferase 6 (HS3ST6), a transmembrane enzyme involved in the synthesis of HS, part of the vascular endothelium infrastructure. HS contributes to the binding of high-molecular-weight kininogen (HK), which then becomes prone to cleavage by kallikrein.[29] Although some experts proposed considering HAE-HSST as BK mediated, the available evidence supports that it is due mainly to vascular endothelium dysfunction (Table I, statement 15).

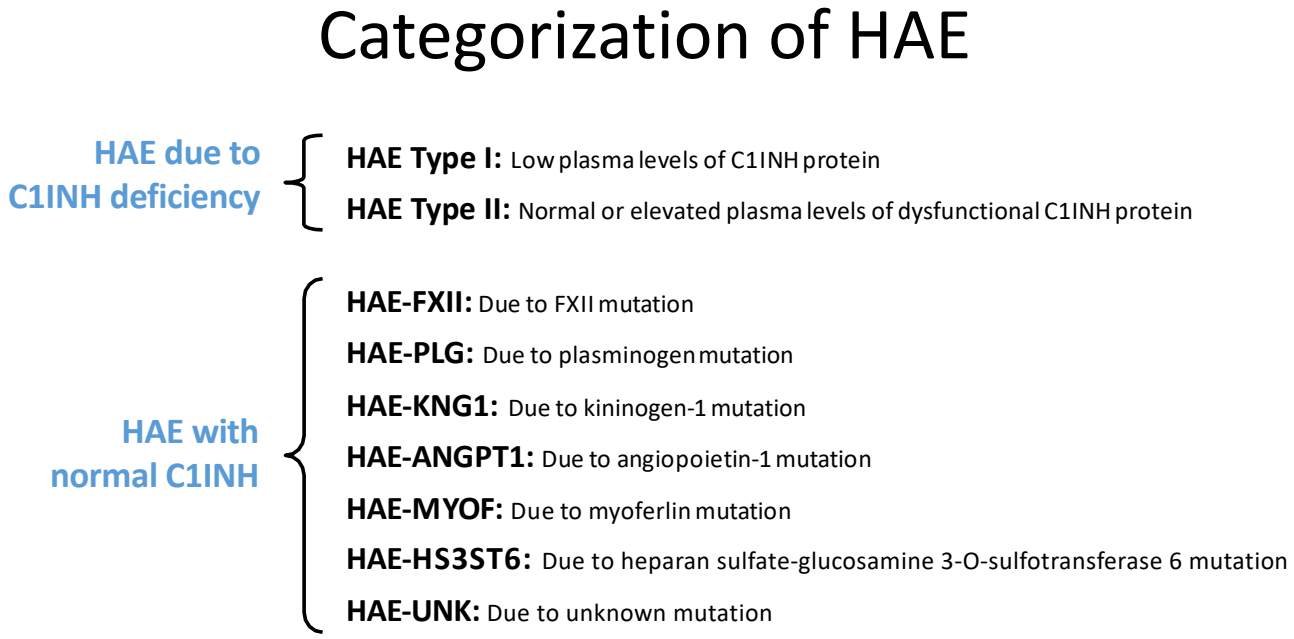

FIG 3. Categorization of HAE.

TABLE III. Consented abbreviations/acronyms, in alphabetic order

Terminology in use	Acronym
Angioedema	AE
Bradykinin-mediated angioedema	AE-BK
Acquired angioedema due to *C1INH* deficiency	AAE-C1INH
Episodic angioedema with eosinophilia	EAE
Drug-induced angioedema	AE-DI
Mast cell–mediated angioedema	AE-MC
Angioedema due to unknown cause	AE-UNK
Angioedema due to vascular endothelium dysfunction	AE-VE
Angioedema due to anaphylaxis	AE-ANA
Angioedema due to normal *C1INH*	HAE-nC1INH
Chronic spontaneous urticaria	CSU
Hereditary angioedema	HAE
HAE due to angiopoietin 1 mutation	HAE-ANGPT
HAE due to *C1INH* deficiency	HAE-C1INH
HAE due to *C1INH* deficiency type 1	HAE-C1INH-Type1
HAE due to *C1INH* deficiency type 2	HAE-C1INH-Type2
HAE due to factor XII mutation	HAE-FXII
HAE due to heparan sulfate 3-*O*-sulfotransferase 6 mutation	HAE-HSST
HAE due to kininogen 1 mutation	HAE-KNG
HAE due to myoferlin mutation	HAE-MYOF
HAE due to plasminogen mutation	HAE-PLG
AE due to nonsteroidal anti-inflammatory drugs	AE-NSAID
AE due to angiotensin-converting enzyme inhibitors	AE-ACEI
AE due to tissue-type plasminogen activators	AE-tPA
AE due to di-peptidyl peptidase IV blockers	AE-DPPIV
AE due to angiotensin receptor–neprilysin inhibitors	AE-ARNI
Systemic capillary leak syndrome	SCLS
Urticaria	URT

Listed are drug families, abbreviations/acronyms, and generic names of drugs in common use implicated in acute and recurrent angioedema attacks.

Systemic capillary leak syndrome is a potentially fatal disorder characterized by unpredicted episodes of extensive AE, causing severe hypotension, hypoalbuminemia, renal failure, muscle necrosis due to compartment syndrome, and life-threatening multisystem failure.[47-49] The pathogenesis of SCLS is held to be driven by endothelial cell dysfunction and subsequent plasma leakage, possibly involving vascular endothelial growth factor, angiopoietin 2, and certain interleukins.[49] Some experts argued that SCLS should not be classified as AE because it often manifests as generalized swelling. However, the majority of the panel voted to include it in the differential diagnosis of AE because it shares similar mechanisms (ie, vascular permeability) and several clinical features similar to HAE.

Drug-induced AE

A new category was created to include all drug-induced AE (AE-DI) because certain drugs can cause severe AE attacks, some of which may be fatal (Table I, statement 16).[50] The underlying pathomechanisms of most drugs listed in this category are unknown; therefore, establishing this distinct category is primarily practical. It aims to help clinicians differentiate AE due to adverse drug reactions (iatrogenic) from other types of AE and thereby avoid further exposure of the patients to the culprit drug or to drugs with similar class effects.

The AE-DI category includes ACE inhibitors (ACEI) and other inhibitors of the renin–angiotensin aldosterone system, including dipeptidyl peptidase IV (DPPIV) and angiotensin receptor–neprilysin inhibitors (ARNI), known triggers for acute drug-induced AE episodes in patients with hypertension, cardiac disease, and/or diabetes (Table I, statement 17).[51-65] Some expert panel members argued that ACEI-induced AE should be designated AE-BK because ACE (kininase II) degrades BK, and BK

levels are increased in patients with AE-ACEI. Similarly, DPPIV inhibitors degrade substance P when ACE is inhibited, increasing the risk of AE in individuals receiving ACEI therapy.[51-54] However, the majority of the panel voted for AE-DI because despite the empirical use of BK receptor antagonist icatibant, it failed to show efficacy in some of the randomized, placebo-controlled trials.[54,55]

Nonsteroidal anti-inflammatory drugs (NSAIDs)[66] and inhibitors of tissue-type plasminogen activator (tPAs) are also known culprits for drug-induced orolingual AE.[67-70] Recombinant tPA is used extensively in ischemic stroke and coronary thrombolysis. The mechanism of AE is still not fully understood, but new data suggest that tPA may trigger HK cleavage and induce BK formation.[71] NSAIDs may trigger AE via eicosanoid pathways or via MC degranulation. Table IV lists pharmacologic agents implicated in acute AE.

AE of unknown cause

AE subtypes for which the pathomechanism or inciting trigger is unknown are classified as AE-UNK (Table I, statement 18). AE-UNK should be differentiated from HAE-UNK; the former is not defined by family history or other consensus clinical criteria, whereas the latter is.[20-22]

The inclusion of a category comprising unknown AE entities reflects an unmet diagnostic need that should inspire further research and yield new findings to enrich the current knowledge base. The DANCE experts recommend that patients with disease diagnosed in this category be followed up and provided the best of care, including off-label therapies judged indispensable by AE experts.

AE-UNK includes episodic AE with eosinophilia (EAE) (Table I, statement 19), a rare disorder characterized by unpredictable attacks of AE and high blood eosinophil levels.[72] Clinical findings include recurrent or nonrecurrent AE, fever, URT, weight gain, blood eosinophilia, and elevated immunoglobulin levels.[73,74] Some evidence points to a contribution of MC to its pathogenesis,[73] or to increased numbers of MCs and serum levels of tryptase. Eosinophil granule proteins were shown (in hamsters) to cause increased vasopermeability independently of MC and histamine, and other cell types, including neutrophils and lymphocytes, might be involved in pathogenesis.[73] Panel deliberations concluded that there is insufficient evidence to support any of these mechanisms, leading to the designation of EAE as AE-UNK.

DISCUSSION

Disease classification systems are essential to introduce order in conceptualizing human health disorders. Nosologic classifications disclose common disease pathophysiology and shared genetic associations, identify new drug targets, and classify disease for diagnostic, prognostic, and treatment decision purposes.[75] Disease classifications should bring on board emerging pathophysiologic, biochemical, and genomic data, making them widely available and easily shared by research networks.[75] Future machine learning may help to increase our understanding of HAE etiology, making it accessible for future applications of personalized medicine.[75]

All AEs covered by the proposed classification are phenotypically expressed by recurrent, localized, and reversible episodes of tissue swelling, regardless of the underlying mechanisms or triggers initiating the attacks. In all types and subtypes of AE, swelling is due to increased extravasation, in which the underlying pathophysiologic target is the vascular endothelium, whose continuity and integrity are breached by internal (ie, BK, histamine) and/or external stimuli (ie, drugs).[8] A large body of evidence supports the notion that such a breach in functional continuity occurs within paracellular mechanisms of the cadherin junction.[3] In all the different AEs, the protein-rich plasma entering the tissues is gradually evacuated after each attack by the local lymphatic system.[3,4] Because AE types are different in their mechanisms and triggering signals, the DANCE classification takes these differences into account and aims to create a unified system covering all currently known AE entities. Such inclusive taxonomy will better assist clinicians in diagnosis and treatment decisions and guide basic research investigators in their efforts to elucidate the mechanisms of unknown diseases.

The DANCE expert panel recognize that AEs are not dichotomous and may have overlapping signatures, so we propose applying the term “endotype” to certain AE types. An endotype is a subtype defined by a distinct functional or pathobiologic mechanism to form a combination of clinical expression, biomarkers, and genetics.[76,77] Such an approach has already proven its usefulness in chronic rhinitis with or without nasal polyposis[3] and in asthma.[78,79]

On the basis of this rationale, the DANCE experts propose to classify MC-mediated AE (AE-MC), BK-mediated AE (AE-BK), and vascular endothelium dysfunction AE (AE-VE) as endotypes, a designation that better reflects their underlying mechanisms, the mediators involved, and the results of genetic cosegregation studies, thereby justifying the existence of a distinct pathobiological entity. We hope this approach helps focus future research in developing targeted treatments and applying personalized medicine to patients.

Less defined conditions, with mechanisms that remain to be elucidated, will be designated as subtypes. This applies in particular to those caused or aggravated by medications (henceforth AE-DI; ie, iatrogenic, drug induced), or AEs with still unknown etiologies (henceforth AE-UNK; ie, idiopathic, unknown). Despite gaps in our knowledge, organizing classes and subclasses of AEs by their underlying mechanisms, although sometimes presumptive, may lead to more accurate diagnosis and better selection of targeted pharmacotherapies.

The most challenging clinical dilemma among clinicians in emergency departments and daily practice is assessing whether a patient’s swelling episode is due to MC mediators or BK. This common diagnostic challenge is particularly important when a decision concerning future treatment needs to be made. AE induced by MC mediators is by far the most frequently observed condition, as in CSU. In the absence of specific biomarkers, AE in CSU without wheals, sometimes referred to as MC-mediated AE, is difficult to diagnose and classify. One approach to the current differential diagnosis excludes other rare causes of recurrent AE and assesses response to antihistamines, corticosteroids, and omalizumab. Some authors argue that patients with AE in CSU without wheals should not be considered to have CSU due to clinical and laboratory differences compared to CSU patients with both recurrent wheals and AE.[80]

Ongoing research efforts aim to identify biomarkers that distinguish AE attributed to the AE-MC endotype from those

TABLE IV. Drugs implicated in angioedema

Drug or drug family	Acronym	Examples	References
Angiotensin-converting enzyme inhibitors (-prils)	ACEI	Enalapril, ramipril, captopril, lisinopril, benazepril, cilazapril	50-60
Angiotensin receptor blockers (-sartans)*	ARB	Losartan, olmesartan, candesartan, telmisartan	51-54
Nonsteroidal anti-inflammatory drugs	NSAID	Aspirin, ibuprofen, naproxen	66
Recombinant human tissue plasminogen activator	rhtPA	Streptokinase, alteplase, tenecteplase	67-71
Dipeptidyl peptidase IV blockers	DPPIV	Sitagliptin, vildagliptin, saxagliptin	62,63
Angiotensin receptor–neprilysin inhibitors	ARNI	Sacubitril	64,65

*ACEI-induced angioedema is not a contraindication to angiotensin receptor blocker therapy.

mediated by other types of AE.[81,82] Additionally, diagnostic algorithms may help establish a correct diagnosis by carefully evaluating the nature of clinical symptoms, family history, response to medications, and laboratory tests, thereby providing clues for clinical diagnosis and management of AE entities.[83]

The global panel of experts agrees that episodic and recurrent AE caused by an increased vascular endothelial permeability deserves to be recognized as a separate nosologic classification. Unified classification, terminology, and nomenclature, along with a widely accepted list of abbreviations/acronyms, are necessary for better diagnosis, clinical decision making, and evidence-based therapeutic strategies. This approach can be challenging, thanks to the significant differences across the globe regarding access to advanced therapeutics, insurance payor systems, and other barriers to diagnosis and care that vary from one country to another. Nonetheless, it is imperative for the development of advanced treatment modalities through clinical trials and future personalized medicine that an agreed-on global terminology for AE disorders be established. Table III and Fig 2 summarize the updated changes in nomenclature and terminology of AE.

This proposed nomenclature system includes AE-UNK because many AE cases still lack substantive data regarding biomarkers, pathomechanisms, or genetics. The DANCE experts are optimistic that additional biomarkers and diagnostics evidence will be available in the future, contributing to a better understanding of AE-UNK. Therefore, we recommend regularly updating this consensus as new evidence on AE types and subtypes becomes available. It is essential to emphasize that the DANCE classification be used in complement with current clinical guidelines and expert consensus recommendations for diagnostic assessment and treatment of AE. They are not meant to replace current clinical guidelines and expert consensus algorithms, and they should not be misconstrued in a way that affects the reimbursement of medicines prescribed by a physician using sound clinical judgment.[20-22,84]

In summary, DANCE has unified the definition, classification, nomenclature, and terminology of AE syndromes, and their use will harmonize and facilitate research, clinical studies, and the development of new medications, which will, we hope, result in improved patient care.

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Key messages

- **Up-to-date comprehensive classification and terminology covering a wide range of AE syndromes was consented by an international team.**
- **This terminology will facilitate diagnosis, research, new medication development, and patient care.**

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TABLE E1. Endorsing professional societies

No.	Acronym	Society
1	AAAAI	American Academy of Allergy, Asthma & Immunology
2	AAAeIC	Argentine Association of Allergy and Clinical Immunology
3	AAIBA	Association of Allergy and Immunology of Buenos Aires
4	ACAAI	American College of Allergy Asthma & Immunology
5	AID	Turkish National Society of Allergy and Clinical Immunology
6	ALaeh	Latin American Association of HAE
7	ALLSA	Allergy Society of South Africa
8	APAAACI	Asia Pacific Association of Allergy, Asthma and Clinical Immunology
9	ASBAI	Brazilian Association of Allergy and Immunology
10	ASCIA	Australasian Society of Clinical Immunology and Allergy
11	BACTA	Bulgarian Alliance of Clinical and Translational Allergy
12	BSA	Bulgarian Society of Allergology
13	CMICA	Mexican College of Clinical Immunology and Allergy
14	DDO	Danish Dermatology Society
15	DGAKI	German Society for Allergology and Clinical Immunology
16	DGIM	German Society of Internal Medicine
17	DST	Dermatology Society of Thailand
18	GA^{2}LEN	Global Allergy and Asthma European Network
19	GAACI	Georgian Association of Allergology and Clinical Immunology
20	GEBRAEH	Brazilian Study Group on Hereditary Angioedema
21	GSAR	German Society for Angioedema Research
22	HAESI	Hereditary Angioedema Society of India
23	HSACI	Hungarian Society for Allergy and Clinical Immunology
24	IAACI	Israeli Association of Allergy and Clinical Immunology
25	IADVL	Indian Association of Dermatologists, Venereologists & Leprologists
26	ITACA	Italian Network on Hereditary and Acquired Angioedema
27	JDA	Japanese Dermatological Association
28	KAAACI	Korean Academy of Asthma, Allergy, and Clinical Immunology
29	KSACI	Kuwait Society of Allergy and Clinical Immunology
30	MAKIT	Hungarian Society of Allergology and Clinical Immunology
31	NDO	Nordic Dermatology Association
32	NIV	Dutch Society for Internal Medicine
33	ÖGDV	Austrian Society of Dermatology and Venereology
34	OSACI	Omani Society of Allergy & Clinical Immunology
35	PDS	Polish Dermatological Society
36	PSA/PTA	Polish Society of Allergology
37	QAIS	Qatar Allergy and Immunology Society
38	RAACI	Russian Association of Allergology and Clinical Immunology
39	RSACI	Romanian Society of Allergology and Clinical Immunology
40	RUBRA	Rede Urticária Brazil
41	SBI	Brazilian Society of Immunology
42	SBP	Brazilian Society of Pediatrics
43	SEAIC	Spanish Society of Allergology and Clinical Immunology
44	SFA	French Society of Allergology
45	SFD	French Society of Dermatology
46	SIAAIC	Italian Society of Allergy, Asthma and Clinical Immunology
47	SIMI	Italian Society of Internal Medicine
48	SLaai	Latin American Society of Allergy and Immunology
49	SORESS	Society of Rhinology and Endoscopic Skull Base Surgery
50	SPAAI	Peruvian Society Allergy, Asthma and Immunology
51	SPDV	Portuguese Society of Dermatology and Venerology
52	TNSACI	Turkish National Society of Allergy and Clinical Immunology
53	UKPIN	United Kingdom Primary Immunodeficiency Network