An expert discussion on the atypical hemolytic uremic syndrome nomenclature—identifying a road map to precision: a report of a National Kidney Foundation Working Group

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The term *atypical hemolytic uremic syndrome* has been in use since the mid-1970s. It was initially used to describe the familial or sporadic form of hemolytic uremic syndrome as opposed to the epidemic, *typical* form of the disease. Over time, the atypical hemolytic uremic syndrome term has evolved into being used to refer to anything that is *not* Shiga toxin–associated hemolytic uremic syndrome. The term describes a heterogeneous group of diseases of disparate causes, a circumstance that makes defining disease-specific natural history and/or targeted treatment approaches challenging. A working group of specialty-specific experts in the thrombotic microangiopathies was convened to review the validity of this broad term in an era of swiftly advancing science and targeted therapeutics. A Delphi approach was used to define and interrogate some of the key issues related to the atypical hemolytic uremic syndrome nomenclature.

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The term hemolytic uremic syndrome (HUS) was first used by Gasser *et al.* in 1955[1] to describe children with hemolytic anemia, acute kidney failure, and thrombocytopenia following an infectious trigger (diarrhea or pneumonia), whereas the term thrombotic thrombocytopenic purpura (TTP) had been first proposed by Singer and Wile in 1947.[2] In subsequent decades, epidemic forms were described mainly in children with diarrhea,[3] and diarrhea-positive forms of HUS were subsequently linked to the Shiga toxin of *Escherichia coli* (STEC).[4] In parallel, non–diarrhea-triggered familial forms of HUS were suggested to be driven by a genetic factor,[5] and to have a particularly severe and recurrent phenotype, with low circulating C3 levels.[6] Growing understanding of the complexity and heterogeneity of HUS led to the terms typical, epidemic, and diarrhea-positive HUS being used for the STEC-associated cases, whereas the terms atypical, sporadic, and diarrhea negative[7] were used for cases in which genetic or serologic dysregulation of the alternative pathway of complement was suspected or identified (as reviewed[8]).

It is difficult to trace when the adjective *atypical* became used as the disease designation instead of simply to describe a clinical phenotype similar to *typical* HUS but for which a preceding diarrheal illness was not identified. However, not long after its introduction into the literature, controversy arose. Authors as early as 1985 had discouraged its use, stating that "recent insights justify a new attempt at classification."[9(p117)] It was clear even at that time that calling a disease *atypical* provided little information about the disease itself and instead only addressed what it was not. Although marginally more descriptive terms have been considered, (sporadic, diarrhea negative,

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nonenteropathic, familial, and recurrent HUS), atypical is the single term that remains in use.[10] It is this term that is currently used by such entities as Online Mendelian Inheritance in Man, Orphanet, and the *International Classification of Diseases* classifications of HUS.

Like typical HUS (a nomenclature that has been replaced by the more precise STEC-HUS term), all atypical HUSs (aHUSs) present with microangiopathic hemolytic anemia, thrombocytopenia, and varying degrees of organ damage, mainly but not exclusively affecting the kidney microvasculature. Reported incidence rates for aHUS are highly variable, depending on a given cohort's inclusion and exclusion criteria, and range from 0.41 to 2.0 cases per million per year.[11,12] Again, our inability to be more precise stems directly from the nomenclature's ambiguity. In fact, not only is aHUS itself heterogeneous, but clinicians have tended to use the nomenclature inconsistently. For example, one group of clinicians may use the term aHUS as it was used in the 1970s (anything that is not STEC HUS),[8] whereas other clinicians use it to refer specifically to HUS driven by uncontrolled activation of the complement system.[13]

Histologically, aHUS is characterized by the presence of a thrombotic microangiopathy (TMA),[14] the picture described 100 years ago by Eli Moschcowitz in his first report of a child with TTP.[15] An important milestone in the history of the TMA syndromes was the ability to more precisely define 2 subcategories of TMA: TTP and STEC HUS. This step was a major advance for both diseases, allowing improved understanding of disease epidemiology and the development of targeted, more effective management. These advances were made possible by the availability of testing for a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) activity and for Shiga toxin. Most other TMA syndromes are captured within the *aHUS* term.[8]

Only modest progress has been made in identifying diagnostic assays for the other forms of TMA. Determining the role of complement is a key element. Even more difficult is the issue of determining whether complement activation is physiological (an immune defense mechanism) or detrimental. Consequently, with the exception of identifying a pathogenic variant in a complement alternative pathway (AP) gene in recurrent aHUS, distinguishing the role of complement as a primary driver of disease as opposed to a secondarily activated system remains challenging. Yet, this distinction may have significant implications for management.

The uncertainty many clinicians face in the clinical management of aHUS is directly related to the ambiguity of the current nomenclature. If *aHUS* defines all forms of TMA that are driven by dysregulation of the AP of complement, then a complement inhibitor should always be used. This is not the case, however, if *aHUS* also includes all non–STEC-HUS, non-TTP forms of TMA for which complement dysregulation is a secondary event or not part of the underlying disease process at all (i.e., for TMA secondary to cyanocobalamin deficiency, or to a genetic variant in the *DGKE* gene). For these reasons, efforts have been made to revise and refine the HUS and/or TMA nomenclature.[8,16–19] All of these efforts agree on the need for an etiology-based classification system, which should be sufficiently fluid to allow regular updating as understanding of the pathophysiology of the spectrum of these conditions evolves. Their main features are shown in Supplementary Table S1.

To investigate potential areas of improvement, a Working Group, convened by the National Kidney Foundation, sought to use a Delphi process to evaluate the key issues surrounding the current aHUS nomenclature. The Working Group's goal was to define the nomenclature's relative strengths and weaknesses and generate recommendations to prepare the field for changing the aHUS terminology. Importantly, this initiative did not seek to revise the current aHUS nomenclature, but rather to identify an incremental approach to improve it.

METHODS

The Working Group was a multidisciplinary group of 24 experts in the management of patients with microangiopathic hemolytic anemia and thrombocytopenia as well as knowledge of the aHUS nomenclature and its use, with representation from adult and pediatric nephrology, complement biology, adult and pediatric hematology, renal pathology, and obstetrics (Supplementary Figure S1). Participants were distributed across 4 Breakout Groups with balanced scientific and clinical expertise in aHUS. Each group functioned as the primary discussant of 1 of 4 topics (Supplementary Figure S2):

- Group A: Describe the history of aHUS and the evolution of the current nomenclature

- Group B: Articulate the rationale for changing the current aHUS nomenclature
- Group C: Highlight the obstacles to change and identify strategies to overcome them
- Group D: Identify potential changes to be made in the current nomenclature and propose a road map for future progress.

The discussion content for each group informed the creation of Delphi statements that were evaluated by the group in its entirety.

The Working Group activities consisted of 4 virtual meetings. The first was a Plenary Session, where presentations prepared the participants for the second phase: 3 virtual sessions, during which the Breakout Groups discussed the advantages and disadvantages of the current aHUS nomenclature and generated recommendations centered around their group topic. The third activity was a Consolidation Session, where the draft recommendations developed by each group were presented and evaluated. In the fourth pursuit, a modified Delphi process[20,21] (Supplementary Figure S3) was used to reach consensus on a suggested approach to modifying the existing aHUS nomenclature.

The Delphi process was guided by a Steering Committee, consisting of the workgroup co-chairs (CMN and MV) and a National Kidney Foundation staff member (DLF), which assembled and refined the draft recommendations from the Consolidation Session and converted them into draft Delphi statements, which were distributed to the Working Group for their review. According to their responses, these statements were refined into final Delphi statements. The final statements were distributed via a Survey Monkey to the Working Group for voting using a 5-point Likert scale: 1, strongly agree; 2, agree; 3, neutral (neither agree nor disagree); 4, disagree; and 5, strongly disagree. Participants were asked to provide rationales for their scores on each statement. All voting was anonymous, and the Steering Committee did not vote.

There were 3 rounds of voting on the Delphi statements. Consensus on a statement was defined by a predetermined response rate of ≥75% of combined responses (agree + strongly agree or disagree + strongly disagree). Statements that did not reach this level of (dis) agreement were modified by the Steering Committee according to the rationales provided in the previous voting round and redistributed with rationales in round 2 voting. In this manner, participants were encouraged to reconsider their previous score. These steps were repeated for each voting round. See Table 1 for a full accounting of the statements and voting results for each round of the Delphi process. Key recommendations were defined as the chief messages resulting from the Delphi process, in the opinion of the Steering Committee members. Subsequently, the manuscript describing this process and its results was shared with 2 patient representatives, whose input was also carefully considered. The following text presents a general summary of the major points that emerged.

RESULTS

Rationale for change

All members of the working group agreed that the atypical hemolytic uremic syndrome nomenclature requires modification. Similar to historical comments, the group agreed that the term *aHUS* provides insufficient information about the underlying disease process. The group also agreed that in an era where our understanding of underlying etiologies is advancing, continued application of the term *aHUS* to many disparate diseases and disease mechanisms limits our ability to build the homogeneous cohorts required to identify prognostic features or disease-specific outcomes for the various subsets of thrombotic microangiopathy. Importantly, this, in turn, limits our ability to establish targeted therapeutics. Furthermore, it was agreed that the term *aHUS* as currently used creates confusion between clinicians, as different clinicians use the term differently. It was clear to the group that creating a more uniform approach to the nomenclature and its use has the potential to advance research and improve patient management.

Although there was 100% agreement that the nomenclature can be improved, the expert panel recognized that the effect of any proposed change on hospital systems, insurance carriers, regulatory agencies, and, most importantly, patients would need to be considered. The collective effort and consensus needed to effect change is a substantial obstacle for change (see below), yet should not impede making initial steps.

The group overwhelmingly recommended that modification of the nomenclature should include discarding the term atypical hemolytic uremic syndrome in favor of a more descriptive term. Because the current term describes what the disease *is not* instead of what it *is* and draws an unnecessary connection with *typical HUS*, a term no longer in use, the group agreed that

Table 1 | The Delphi process used to obtain consensus within the working group

Statements	Consensus vote[a]	
Round 1	Consensus %	Agree/ disagree
Rationale for considering a change in the nomenclature[b]		
1. The aHUS nomenclature requires modification.	100	Agree
2. The term atypical hemolytic uremic syndrome should be discarded as it does not reflect underlying pathology.	82	Agree
3. The terms primary and secondary should no longer be used to categorize the TMA syndromes.	50[c]	*
4. The term aHUS is a nonspecific term that encompasses many, disparate diseases.	86	Agree
5. The term aHUS limits our ability to build homogeneous cohorts required to identify prognostic features or disease-specific outcomes for the subsets of thrombotic microangiopathy.	86	Agree
6. The term aHUS provides insufficient information about the underlying disease process to guide treatment.	96	Agree
7. The nonspecific nature of the term aHUS has the potential to confound research by allowing for heterogeneous research cohorts.	91	Agree
8. The term aHUS has the potential to create confusion between clinicians as different clinicians use the term differently.	96	Agree
9. An anticipated benefit to a change in the nomenclature is the ability to more precisely categorize patients.	100	Agree
10. The movement to a nomenclature based on underlying disease mechanism would allow for the development and deployment of more targeted therapeutics.	86	Agree
11. One advantage to keeping the current aHUS nomenclature is that it allows access to terminal complement blockade in cases where it is uncertain to what degree complement activity is playing a role in disease.	41[c]	*
Obstacles to a change of the nomenclature		
12. A major challenge to a change in the aHUS nomenclature includes the lack of widely available diagnostic assays.	86	Agree
13. A major challenge to a change in the aHUS nomenclature includes the lack of highly sensitive, validated diagnostic assays.	73[c]	*
14. A major challenge to a change in the aHUS nomenclature includes patient reluctance to the change.	46[c]	*
15. A major challenge to a change in the aHUS nomenclature is our inability to define the underlying etiology of many of the TMAs.	59[c]	*
16. A major challenge to a change in the aHUS nomenclature is the current acceptance of the term aHUS by regulatory bodies and third party payers.	68[c]	*
Ideal characteristics of a nomenclature		
17. A more appropriate umbrella term for the aHUS nomenclature is thrombotic microangiopathy.	64[c]	*
18. A more appropriate umbrella term for the aHUS nomenclature is microangiopathy.	59[c]	*
19. A more appropriate umbrella term for use is hemolytic uremic syndrome.	73[c]	*
20. A more appropriate umbrella term for the aHUS nomenclature is endotheliopathy.	64[c]	*
21. A more appropriate umbrella term for the aHUS nomenclature is microangiopathic kidney injury.	59[c]	*
22. The term chosen for the aHUS nomenclature must apply whether or not a kidney biopsy is available.	82	Agree
23. The role of a given disease driver may be different in the acute vs. the chronic phase of disease.	64[c]	*
24. The disease designation should be preceded by a qualifier (i.e., viral induced, drug induced), when known or suspected.	91	Agree
25. In the case of qualifiers, a standard list of qualifiers should be considered as part of the nomenclature.	96	Agree
Research considerations		
26. An ability to precisely identify the underlying disease mechanisms will be required before a nomenclature change is possible.	50[c]	*
27. An ability to precisely identify the role of complement in different forms of disease will be required before a nomenclature change is possible.	55[c]	*
28. Currently available diagnostic tools are insufficient to define the role of complement in different phases of the disease (acute vs. chronic).	68[c]	*
29. Currently available diagnostic tools are insufficient for clarifying whether a disease will be sensitive to complement inhibition or not.	68[c]	*
30. The identification of a pathogenic complement gene variant or a high-titer FH autoantibody should be the sole criterion for confirming the role of complement in disease.	91	Disagree
31. The identification of a complement gene variant of unknown significance is insufficient to confirm the role of complement in aHUS.	82	Agree
32. The absence of a complement gene variant does not rule out complement-mediated HUS.	96	Agree
Features of an improved nomenclature		
33. A preferred HUS nomenclature would include a term designating the main underlying disease mechanism/etiology.	95	Agree

Table 1 | (Continued) **The Delphi process used to obtain consensus within the working group**

Features of an improved nomenclature		
34. A preferred aHUS nomenclature would include a term that acknowledges response/lack of response to complement blockade.	55[c]	*
35. A preferred aHUS nomenclature would include a term defining whether or not complement is involved acutely or chronically in the disease pathogenesis.	55[c]	*
36. A preferred aHUS nomenclature would include a term acknowledging the trigger to disease when known.	73[c]	*
37. A preferred aHUS nomenclature would include a term that describes the risk for relapse when known.	64[c]	*
38. A preferred aHUS nomenclature would include a designation for specific organ(s) involved.	14[c]	*
39. A histologic examination (i.e., kidney biopsy) is strongly recommended to secure the diagnosis of aHUS	32[c]	*
40. Evidence of microangiopathic hemolytic anemia (hemolysis, thrombocytopenia, and schistocytes) is required for the aHUS diagnosis.	50[c]	*
41. Overt renal injury is not required to make the diagnosis of aHUS.	41[c]	*
42. Bone marrow transplant should be considered a trigger when *de novo* aHUS occurs after BMT.	77	Agree
Statements	**Consensus vote[a]**	
Round 2 (X)[d]	**Consensus %**	**Agree/ disagree**
1. (3) Rather than categorizing TMAs as primary or secondary, an etiology-based classification would be more helpful in the management of different forms of TMA.	100	Agree
2. (11) The use of a new nomenclature to replace aHUS should be implemented, being mindful of the necessity to maintain the possibility of access to complement inhibition, not only for clearly complement-driven TMA, but also in forms in which complement involvement is less easy to establish, particularly in an emergency setting.	82	Agree
3. (13) A major challenge to a change in the aHUS nomenclature includes the lack of highly sensitive, validated diagnostic assays. However, this should not preclude moving forward with a change that can be further refined as our understanding of the underlying etiology improves.	100	Agree
4. (14) Some patients with aHUS may be reluctant to change the definition of their disease. However, if the change led to improved access to correct treatment and patient involvement were part of the process, this reluctance could be overcome.	82	Agree
5. (15) A major challenge to a change in the aHUS nomenclature is our inability to rapidly define the underlying etiology of many of the TMAs in an emergency setting. However, this should not preclude moving forward with a change that can then be further refined as our understanding of the underlying etiology improves.	91	Agree
6. (16) A challenge to a change in the aHUS nomenclature is the current acceptance of the term aHUS by regulatory bodies and third-party payers. Despite this, a more correct new nomenclature should still be proposed and implemented.	96	Agree
7. (17) A more appropriate umbrella term for nomenclature encompassing aHUS/TTP/typical HUS is *thrombotic microangiopathy*, to be used in combination with qualifiers whenever possible.	86	Agree
8. (18) The nomenclature *microangiopathy* alone as an umbrella term for all the aHUS/TTP/typical HUS conditions is too broad.	73[e]	*
9. (19) The terminology *hemolytic uremic syndrome* is not an appropriate umbrella term for classification purposes.	68[e]	*
10. (20) The nomenclature *endotheliopathy* as an umbrella term for all the aHUS/TTP/typical HUS conditions is too broad.	82	Agree
11. (21) The nomenclature *microangiopathic kidney injury* as an umbrella term for all the aHUS/TTP/typical HUS conditions is too broad.	55[e]	*
12. (23) Complement involvement/dysregulation may be acute or chronic in different forms of TMA syndromes.	96	Agree
13. (26) The term aHUS can be eliminated even in the absence of understanding the underlying disease mechanism for all presentations.	73[e]	*
14. (27) The ability to define the role of complement in the different forms of disease is not a prerequisite for changing the nomenclature.	86	Agree
15. (28) Currently available diagnostic tools are insufficient for defining the role of complement in different forms of disease.	91	Agree
16. (29) Currently available diagnostic tools are insufficient for clarifying which forms of the disease will be sensitive to complement inhibition.	82	Agree
17. (34) Response to complement inhibition should be included in a new nomenclature for this disease. Use this option.	46[e]	*
18. (35) If known, acute or chronic complement activation should be included in a new nomenclature for this disease.	50[e]	*
19. (36) A preferred aHUS nomenclature would include a term acknowledging the trigger to disease when known.	82	Agree
20. (37) An updated nomenclature does not require a term for risk for relapse.	82	Agree
21. (38) At this point in the nomenclature discussion, a term for designating the organ involved is not required.	68[e]	*
22. (39) A kidney biopsy is useful but not required to confirm the diagnosis of aHUS.	86	Agree
23. (40) Either a clinical microangiopathic hemolytic anemia or a thrombotic microangiopathy on biopsy must be present to diagnose aHUS.	82	Agree
24. (41) Clinically evident renal injury is not required for the diagnosis of aHUS.	50[e]	*

(*Continued on following page*)

Table 1 | (Continued)

Round 3	Consensus %	Agree/ disagree
1. The term *hemolytic uremic syndrome* is not an appropriate umbrella term for the classification of all conditions characterized by thrombotic microangiopathy.	100	Agree
2. The nomenclature *microangiopathic kidney injury* is not an appropriate as an umbrella term for all the aHUS/TTP/HUS conditions	100	Agree
3. Response to complement inhibition should be included in a new nomenclature for aHUS, provided the response may be accurately determined.	73	*
4. A new nomenclature for aHUS should include a designation for the presence of complement gene abnormalities of import when such gene presence has been identified.	86	Agree
5. A new nomenclature of aHUS does not required organ involvement (i.e., renal only, systemic only, etc.).	82	Agree
6. A nomenclature using *TMA* instead of *HUS* as the umbrella term would have the advantage of including forms of disease in which clinically evident renal injury is not present.	82	Agree

aHUS, atypical hemolytic uremic syndrome; FH, factor H; HUS, hemolytic uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.
[a]Consensus includes a combined score for strongly agree and agree.
[b]Identifies the general category of statement.
[c]No-consensus statements for round 1 (consensus score, <75%, denoted by *) were modulated on the basis of expert input and moved forward to round 2.
[d]The number in parentheses identifies statement from previous round.
[e]No-consensus statements for round 2 (consensus score, <75%, denoted by *) were modulated on the basis of expert input and moved forward to round 3.

selecting an alternative is a logical step forward. Similar to the change of *typical* HUS to STEC HUS, the group agreed that, whenever possible, a uniform nomenclature reflecting the underlying trigger or mechanism of disease would be substantially more useful.

Obstacles to change

The first major challenge to a change in the aHUS nomenclature includes the lack of widely available diagnostic assays to identify different causes. Importantly, despite this obstacle, the group agreed that it was time to begin iterative changes in the nomenclature. Although there is much to learn about underlying disease mechanism for many of the TMAs, the group did not think that, before improving the nomenclature, it was necessary to have tools to precisely identify each of the underlying disease mechanisms for patients manifesting the aHUS clinical/histologic picture. Similarly, being able to precisely determine whether complement was a pathologic driver for some or all of the TMAs (whether in the acute or chronic setting) should not be a prerequisite to nomenclature modification.

Other obstacles to change were identified, including the current acceptance of the nonspecific term *aHUS* as a specific disease entity by regulatory bodies, pharmaceutical companies, medical care systems, and third-party payers. A nomenclature change will require careful management through policy and diagnostic code changes.

Similarly, providers and patients will require education on the significance of a new nomenclature. Of particular note are patients who at one moment carry the aHUS diagnosis and who then inherit the changed diagnosis. These individuals must be assured that this change will not adversely affect their access to state-of-the-art care. The Working Group recognized that patients caught in the midst of a change may find it challenging to understand what it means for them. We are encouraged by the fact that historically, nomenclature change has occurred for most diseases, as improved understanding of the underlying pathophysiology has allowed a nomenclature reflecting this to be established. An example of this in the field of nephrology has been IgA nephropathy, originally defined Berger nephropathy from the name of the first physician to describe it.

Crucially, the group recognized the concern patients may have around the potential that a change in terminology may hinder timely approach to life-saving treatment. This is exactly what the use of correct terminology must avoid. The goal for treatment for all patients should be timely targeted therapy. The rationale of keeping an outdated, nonspecific terminology simply to facilitate the use of nontargeted treatment approaches was deemed insufficient.

While fully recognizing these potential obstacles, the group agreed that change is necessary and will trigger an opportunity to educate all relevant stakeholders on the value of the nomenclature update and the potential for scientific progress with a more accurate terminology.

Considerations for choosing a new nomenclature

The Working Group strongly agreed (93% agreement) that the most important aspect of a preferred nomenclature would be the inclusion of a term designating the main underlying disease mechanism/etiology. Although this is ideal, the group recognized that the science of defining underlying etiology is insufficiently mature to easily categorize all entities precisely. However, they recognized the value this step provided for management of TTP and STEC HUS and, therefore, agreed on this goal. When etiology is unclear, there was a general consensus (82% agreement) that the most appropriate umbrella term currently may be thrombotic microangiopathy (TMA). TMA was favored over HUS by most group members because the group recognized that disease presentation is sometimes not accompanied by overt renal injury, making the term HUS not always appropriate. Because the disease as currently defined is always a TMA, the term TMA seemed to be an acceptable first step. Terms such as microangiopathy, endotheliopathy, and microangiopathic kidney injury were also considered.

Moreover, the TMA term is accompanied by clear diagnostic criteria, is vastly used in common practice worldwide, and offers a histologic or clinical description of well-defined disease characteristics. Importantly, this term encompasses forms that do not have a predominant kidney involvement, leading smoothly to a differential diagnosis with TTP and with many other forms, such as bone marrow transplant–associated TMA, in which kidney involvement can be subtle. It also allows for the inclusion of forms that do not present overt microangiopathic hemolytic anemia but rather isolated histologic lesions, as can be seen in kidney-limited TMAs.[19]

There was general agreement that where possible, the disease designation should be preceded by a qualifier (i.e., viral-induced TMA, drug-induced TMA), when etiology is known or firmly suspected. This approach was felt to best support potential management approaches (i.e., the timely discontinuation of a suspected drug). In the case of qualifiers, a standard list should be considered as part of the nomenclature modification process. Figure 1 shows a sample listing and categorization of TMA qualifiers and a suggested approach to formulating a working diagnosis. A nomenclature based on underlying etiology could be the premise for development of more targeted testing and more tailored therapeutics and may have the potential to facilitate and stimulate further research.

The Working Group acknowledged that several gray areas exist when considering changing the aHUS terminology, particularly regarding the pathogenic role of complement. Currently, the identification of an AP complement gene variant of unknown significance is insufficient to confirm the role of complement in a patient with TMA. Similarly, the absence of an AP complement gene variant may not rule out complement-mediated TMA. Moreover, the term *complement-mediated* does not reflect whether the role of complement is temporary and physiological (i.e., during infection) or the main driver of TMA, such as in complement dysregulation–induced TMA attributable to AP pathogenic variants or anti–factor H antibodies. To address this uncertainty, more precise qualifiers could easily be added over time as the new nomenclature evolves (e.g., gemcitabine-induced TMA would replace the more general drug-induced TMA when this etiology is confirmed). In this way, iterative changes could be made in the nomenclature without waiting for a full body of science, but also avoiding unnecessary inaccuracies.

Further nomenclature considerations include that the ultimate term chosen must apply whether or not a tissue biopsy is available. This is an important distinction, because TMA was originally coined as a histologic term, not a clinical term, although it is now used in this setting.

The Working Group recommended that the terms primary and secondary should no longer be used to categorize the TMA spectrum. Additionally, there was support within the group to favor as qualifier the main driver of the disease rather than the trigger when possible. For example, the appropriate terminology for infection-triggered disease in a patient carrying a pathogenic C3 gene variant would be complement-mediated TMA (not infection-related TMA). In a real-world setting, the exact disease designation of a single patient is a work in progress, with an initial diagnosis being made on the basis of clinical presentation (e.g., based on an identifiable trigger), whereas subsequent results may reveal the underlying etiology (e.g., a complement pathogenic variant). Therefore, the nomenclature needs to be fluid, allowing for qualifiers to be added or substituted as understanding progresses. Similarly, extended discussion addressed the potential benefit of including a relative

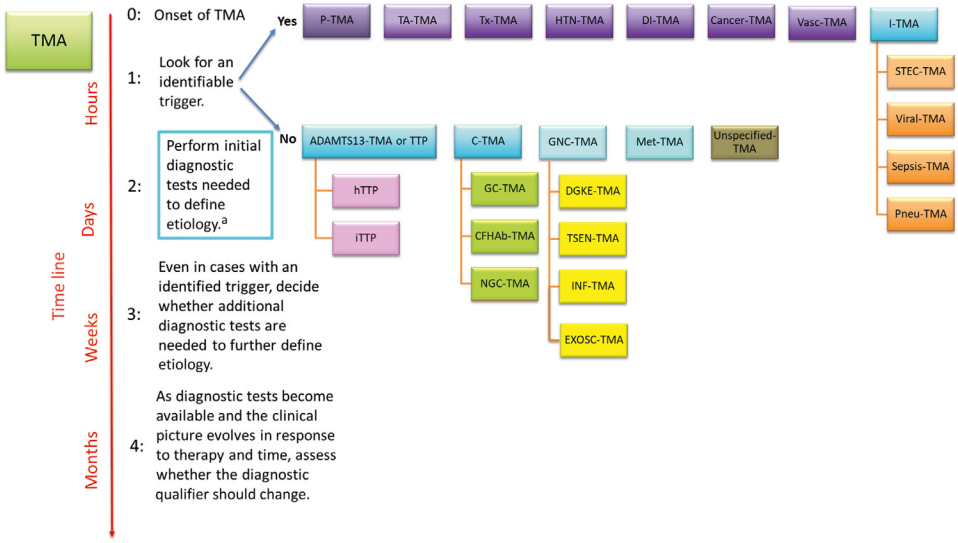

Figure 1 | A model of how a nomenclature based on etiological qualifiers might evolve, grouping all entities as forms of thrombotic microangiopathy (TMA). Identifying the etiology of different forms of TMA is a process. The diagnosis may change as more information becomes available. For the forms in which a trigger is identifiable, underlying conditions, such as genetic predispositions, complement dysregulation, and metabolic disease etc., may well be diagnosed over time. Patients with an underlying complement dysregulation, for example, often require a trigger for TMA to manifest itself. Therefore, the categorization is meant to be fluid. This model is not meant to exclude a role for complement, at least in part, in any of the TMAs. The basic requisite diagnostic examinations will change as our understanding advances, but for now include the following: [a]Shiga toxin of *Escherichia coli* (STEC) serology, urinary *Streptococcus pneumoniae* (Pneu) soluble antigen, a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) activity, complement alternative pathway genetic variant screening, circulating anti–factor H (FH) antibody levels, diacylglicerol kinase epsilon (DGKE) genetic variant screening, circulating homocysteine levels, and urinary organic acid dosing. Cancer-TMA, neoplasm-associated thrombotic microangiopathy; CFHAb-TMA, thrombotic microangiopathy driven by anti–complement FH antibodies; C-TMA, complement-mediated thrombotic microangiopathy; DI-TMA, drug-induced thrombotic microangiopathy (a qualifier may be added when an exact drug is identified); GC-TMA, genetic complement-mediated thrombotic microangiopathy (i.e., with a known pathogenic variant); GNC-TMA, non–complement-related known pathogenic variant in other genes (*DGKE*, *TSEN*, *INF*, *EXOSC*, etc.) thrombotic microangiopathy; HTN-TMA, malignant hypertension-induced thrombotic microangiopathy; hTTP, hereditary thrombotic thrombocytopenic purpura; I-TMA, infection-associated thrombotic microangiopathy; iTTP, immune thrombotic thrombocytopenic purpura; Met-TMA, metabolic thrombotic microangiopathy (cyanocobalamin deficiency); NGC-TMA, complement-mediated thrombotic microangiopathy with no known pathogenic variant; P-TMA, pregnancy-associated thrombotic microangiopathy; TA-TMA, bone marrow transplant–associated thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; Tx-TMA, solid organ (mostly kidney) transplant-associated thrombotic microangiopathy; Vasc-TMA, vasculitis-associated thrombotic microangiopathy.

response to complement therapy as an aspect of the nomenclature (i.e., defining a disease entity as *terminal complement blockade–responsive TMA*). Ultimately, the group could not reach consensus on this issue (73% with agreement), mainly because of the lack of solid criteria for definition of response to terminal complement blockade.

Although there was considerable discussion, 91% of the group agreed that the term "*complement-mediated*" TMA as a substitute for *aHUS* should not be used only when a pathogenic AP complement gene variant or a high titer factor H autoantibody was identified. This reluctance highlights an insufficient scientific understanding of the role of the different complement pathways in many forms of TMA at this stage and the fact that, at present in ≈40% of patients with complement-mediated TMA, neither pathogenic gene variants nor anti–factor H autoantibodies are detected.

Additional qualifications for a newly devised nomenclature included that it need not describe risk for relapse or organ involvement or require a biopsy or histologic examination, and that overt evidence of kidney injury need not be present.

DISCUSSION

It was the consensus opinion of this global expert panel that it is time to modify the aHUS nomenclature. The field has been plagued long enough by what Drummond[9(p118)] described as a "failure to recognize the heterogenous nature of hemolytic uremic syndrome and to distinguish different diseases leading to the syndrome, making it difficult to demonstrate important advances in therapy." The panel recognized that, nearly 40 years later, an important opportunity is upon us.

The rationale for change has both a qualitative and a quantitative logic. In an era where the medical community strives for precise

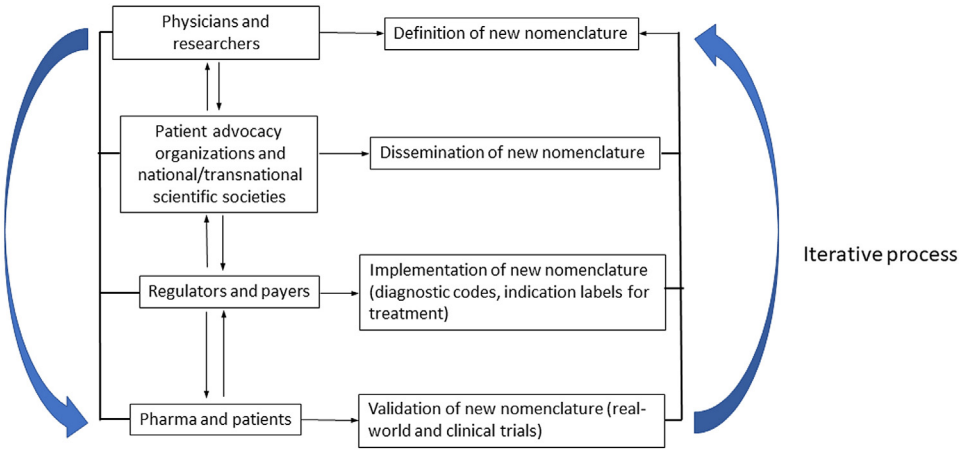

Figure 2 | A model of how a new nomenclature might be implemented in the real world, involving all the relevant stakeholders. Pharma, pharmaceutical companies.

definitions and targeted therapeutics, the term *atypical* is a grossly vague descriptor of a whole collection of diseases and fails to recognize the multiple potential causes that are currently housed within the term. Compounding this issue is the fact that the term aHUS means different things to different clinicians, opening the door to confusion in diagnostic and treatment approaches.

Although we have collaborated on laying the groundwork for a revised nomenclature of the various subtypes of aHUS, we recognize that more discussion is necessary before this can be completed successfully. The group acknowledged that this will be an iterative process and sought primarily to devise a road map for relevant stakeholders and to define some of the critical tasks toward making the change successfully (Figure 2).

The following key recommendations and suggestions have been made for next steps:

(i) The aHUS nomenclature should be modified.
(ii) A more appropriate umbrella term for the aHUS nomenclature at this time is TMA.
(iii) The disease designation should be preceded by a qualifier describing the underlying etiology when known or strongly suspected.
(iv) Future research should focus on precisely identifying the role of complement in individual disease entities.
(v) Future research should also focus on defining more precisely the role of potential triggers in TMA onset.

Although the expertise of the convened specialists was fairly broad, it is likely that there is other expert opinion on this issue. Similarly, although comments received from patients were given careful consideration in the preparation of this report, there has been only limited patient and patient representative review of this discussion, and that will need to follow. Finally, each of the Working Group members agreed that we must recognize that the scientific underpinnings of a perfect nomenclature are simply not available yet. Nonetheless, it was the general consensus that incremental improvements are a laudable goal, and that our initial proposal may pave the way for further progress as our understanding of underlying etiologies evolves.

DISCLOSURE

CMN has received either clinical trial research or advisory board funding from the following: ChemoCentryx, Novartis, Retrophin, BioCryst, Apellis, Achillion, Alexion, Silence Therapeutics, Kira, and UpToDate. RB has served on advisory boards for Alexion, AstraZeneca Rare Disease, UCB Biosciences, Comanche Biopharma, and Roche Diagnostics. He has also participated in sponsored clinical trials and serves on the speaker's bureau for Alexion and AstraZeneca Rare Disease. SCh received honoraria from Sanofi and Takeda for internal education; received consulting fees for advisory boards from Sanofi, Takeda, Alexion, and Sobi; and participated on advisory boards for Alexion and Sanofi. HTC has received consulting fees from Novartis Pharmaceuticals. AC has served as a consultant for MingSight, Sanofi, and Synergy; and has received authorship royalties from UpToDate.

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Supplementary material is available online at www.kidney-international.org.

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