Pharmacological Research 216 (2025) 107714

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Multidisciplinary consensus on the diagnosis and management of patients with atypical Hemolytic Uremic Syndrome (complement-mediated TMA): Recommendations from Italian scientific societies, patient associations and regulators

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Abbreviations: ADAMT13, A Disintegrin and Metalloproteinase with Thrombospondin motifs von-Willebrand Factor proteinase; AHUS, atypical hemolytic uremic syndrome; ANA, anti-nuclear antibodies; AP50, 50 % alternative pathway; C3, component 3; C4, component 4; C5, component 5; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; CAP, complement alternative pathway; CFH, complement factor H; CH50;, 50 % hemolytic complement; CoReMaRs, Regional Rare Diseases Coordinating Centres; DGKE, diacylglycerol kinase epsilon; Ds-DNA;, double-stranded DNA; DTCP, Diagnostic and Therapeutic Care Pathway; EEG, electroencephalogram; ENA, extractable nuclear antigen; FLAIR, fluid-attenuated inversion recovery; GP1, glycoprotein 1; H-MEC, human microvascular endothelial cells; HUS, hemolytic uremic syndrome; ICU, intensive care unit; Ig, immunoglobulin; INR, international normalized ratio; LAC, Lupus anticoagulant; LDH, lactate dehydrogenase; MAb, monoclonal antibody; MDT, multidisciplinary team; MLPA, Multiplex ligation-dependent probe amplification; MRI, magnetic resonance imaging; MTOR, mammalian target of rapamycin; NGS, next generation sequencing; P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PAs, Patient Associations; PTT, partial thromboplastin time; RD, rare disease; STEC-HUS, Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome; SSs, Scientific Societies; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VTEC, verocytotoxin-producing *Escherichia coli*.

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https://doi.org/10.1016/j.phrs.2025.107714
Received 11 December 2024; Received in revised form 19 March 2025; Accepted 24 March 2025
Available online 9 April 2025

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ARTICLE INFO

Keywords:
Atypical hemolytic uremic syndrome
Delphi consensus
Multidisciplinary care
Patient-centered approach

ABSTRACT

Atypical Hemolytic Uremic Syndrome (aHUS) is a severe, systemic, rare disease (RD) that can occur in people of all ages, and is associated with high rates of morbidity and mortality. Because the management of patients with aHUS can be difficult, more effective strategies should be implemented. Faculty members from several Italian Scientific Societies, Patient Associations and Regional Institutional Experts on RDs met to discuss aHUS management within a multidisciplinary team (MDT), using a Delphi process to develop consensus recommendations. Consensus (≥70 % agreement by faculty members) was reached on 51 statements with the aim of improving patient management and outcomes. These statements provide a unified framework for the differential diagnosis of aHUS, prompt recognition of the pathology, referral to RD reference centers, selecting between treatment relapse prevention measures options, patient management by a MDT and improving the overall awareness of aHUS. Despite the broad scope of the consensus statements, several unmet needs in the management of patients with aHUS were identified, including diagnostic suspicion, rapid genetic investigations, regular review of the centers of expertise (considering the number of treated patients), permanent clinical referral in treatment centers and widespread expertise among adult and pediatric specialists. We hope that this standardized framework will form the basis of the "digital ecosystem" concept and development of possible information technology solutions to assist the MDT involved in the management of patients with aHUS.

1. Introduction

Atypical Hemolytic Uremic Syndrome (aHUS; ORPHA:2134) is a severe, systemic, rare disease (RD). The underlying factors of this form of thrombotic microangiopathy (TMA) include a key role played by genetic and/or immunologic backgrounds and environmental trigger factors, which together, and to varying degrees in each case, lead to dysregulated activation of the complement alternative pathway (CAP) [1]. This process results in the development of systemic endotheliosis, characterized by the expression of prothrombotic vascular factors, which in turn leads to the formation of platelet microthrombi that underlies mechanical hemolysis [2].

Like other types of TMAs, aHUS is characterized by intravascular hemolytic anemia, platelet consumption, and ischemic organ damage, especially in the kidneys. Indeed, the diagnosis is clinical and involves excluding other forms of TMA, making it one of the more complex aspects of the diagnostic process [1,2].

The precise global prevalence and incidence of aHUS are still

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unclear; nevertheless, current estimates indicate a prevalence of 2.2–9.4 cases per million people aged 20 years and older [3]. Populations in Europe/Oceania have the most epidemiological references, reporting an incidence of 0.2–1.9 per million inhabitants per year and a prevalence of ~5 patients per million total population in Europe [4]. A recent analysis of the population in the Lombardy region of Italy (comprising 9.6 million inhabitants, of which 1.6 million were under 18 years of age) reported an annual incidence of 6.3 cases of HUS per million children, with the incidence rising to 15.7 cases per million among children under 5 years old; of these, 11.9 % were attributed to aHUS [5].

Although initially considered a disease that presents in childhood, aHUS can occur at any age; a study of 851 patients with aHUS found that the mean age at initial presentation was 21. 4 years [6]. High rates of morbidity and mortality were observed in patients with aHUS before the introduction of anti-complement protein C5-antibody therapy, which dramatically improved the disease's natural history [7–9].

Many factors are barriers to the diagnosis and treatment of aHUS. Diagnostic delay is often attributed to a limited understanding of the disease, the complex and heterogeneous nature of presentation, and the involvement of multiple organs [10–12]. Other factors include the failure to carry out specific assays (that are essential for a differential diagnosis) at many centers and the lack of Diagnostic and Therapeutic Care Pathways (DTCPs) involving various professionals [13,14].

Therefore, early recognition, diagnosis and prompt referral to a center for RDs are critical and are likely to result in overall cost-savings [15–17]. Early diagnosis is particularly crucial as this avoids clinical deterioration, allows for appropriate and effective treatment to be selected and prevents worsening clinical conditions due to diagnostic uncertainty [18]. Vande Walle et al.[19] demonstrated that initiating therapy with anti-C5 humanized monoclonal antibodies (mAbs) within the first 7 days of disease onset allows for a more rapid normalization of platelet counts and a more significant, rapid, and sustained improvement in renal function parameters [19].

Since thrombotic thrombocytopenic purpura (TTP), aHUS and other forms of HUS are distinct types of TMAs that share similar clinical and pathophysiologic presentations, their investigation and subsequent diagnosis and management should be clearly defined [20–22]. Once other causes of TMA have been excluded, aHUS is diagnosed if thrombocytopenia and hemolytic anemia are present with renal involvement [3,23].

In light of the heterogeneity of the clinical presentation and systemic involvement of aHUS, more than one specialist is often involved in patient diagnosis and management [24–26]. Management of patients with aHUS by a multidisciplinary team (MDT) is recommended to improve prognosis [27].

Since aHUS can be caused by genetic or acquired (autoantibodies) abnormalities in the CAP [2,23,28,29], its treatment involves the use of recombinant humanized mAbs that bind to C5 thereby preventing its cleavage, which ultimately leads to inhibition of terminal complement-mediated intravascular hemolysis [30–33]. Two anti-C5 mAbs, eculizumab (short-acting), and ravulizumab (a newer long-acting agent), are currently available in Italy for the treatment of aHUS [34,35]. Clinical evidence shows that thrombocytopenia and extra renal symptoms improve rapidly after the first dose of eculizumab [36].

In our experience, many physicians are unfamiliar with assessing and diagnosing aHUS and effectively implementing the strategies needed to manage patients with aHUS. Therefore, we aimed to use a Delphi process to develop consensus recommendations harmonizing the approach of different RD branches of several Italian Scientific Societies (SSs), Patient Associations (PAs), and Regional Institutional Experts on RDs (CoReMaRs), to diagnose, manage, treat and facilitate care within a MDT and to ensure therapeutic appropriateness for patients with aHUS.

2. Methods

A Delphi process was conducted to identify key topics and subtopics for the consensus statements, define questionnaire sections, select groups to develop the consensus statements, and then vote on the statements. The faculty members who participated in the Delphi consensus process included presidents and delegates from 11 Italian SSs, 2 PAs, and 2 CoReMaRs (25 participants from Italian SSs, 3 from PAs, and 4 from CoReMaRs) who were experts in a variety of specialist medical fields: rare diseases, clinical and molecular medicine, internal medicine, nephrology, dialysis, transplantation, immunohematology, transfusion medicine, pediatrics, neuroscience, neurology, rheumatology, surgery, emergency medicine, medical science, precision medicine, and pharmacology.

After an initial meeting held on 20 July 2023 to discuss the methodology of the Delphi process, faculty members (multiple members from each SS, PA, or CoReMar; n = 25) were asked to draft consensus statements based on within-group literature searches and their knowledge and clinical experience, bearing in mind eight key concepts (interdisciplinarity, multidimensionality, digitization, best practice, relationships between health care providers, awareness and early diagnosis, involvement of patient quality of life, and training/information; Supplementary Table S1). LG, EDS, and a methodologist reviewed and standardized the statements, and grouped them into 7 topics: (i) definition (2 items); (ii) diagnosis (12 items); (iii) symptoms and laboratory data (7 items); (iv) prevention (3 items); (v) treatment (9 items); (vi) patient management (11 items); and (vii) awareness (7 items). The statements were then emailed to the faculty members (experts on the panel) who were asked to rate their agreement with each statement on the following scale: 1 =strongly disagree, 2 =disagree, 3 =neither agree nor disagree, 4 =agree, and 5 =strongly agree. Participants could also provide free-text feedback on the statements. Consensus was considered to be achieved if ≥ 70.0 % of the panel gave the statement a score of ≥ 4. Participating SSs, PAs, or CoReMars expressed at least one vote (n = 25).

After the first round of voting, a second meeting was held on 6 February 2024 in Milan to discuss the results, revise (for statements where consensus was not met) and finalize the 51 consensus statements. The statements were then re-circulated for a second round of voting, where each participating SS, PA, or CoReMar was allowed one vote only (n = 14).

3. Results

Consensus was reached for 51 statements (Table 1).

3.1. Definition of aHUS

aHUS can be defined as a rare, systemic, life-threatening disease characterized by non-immune hemolytic anemia, thrombocytopenia, and renal involvement (consensus statement 1). aHUS is a multifactorial disease characterized by a combination of genetic or acquired abnormalities (anti-CFH antibodies) that affect the CAP and the presence of a triggering background (consensus statement 2). Triggers are required for disease manifestation because of the incomplete penetrance of complement gene mutations [28]. The most frequent triggers reported are infections and pregnancy [37] but the triggering background encompasses a broad range of factors and clinical conditions that can variably unmask the disease [1,3]. Triggering factors often complicate the diagnostic process, and may also lead to a secondary form of HUS, which is clearly associated with a specific pathogenic agent. However, in secondary forms of HUS, the condition typically goes into remission upon the removal of the causative agent (medications, infections). If remission does not occur, the diagnosis of a secondary form of HUS should be re-evaluated, considering the underlying factors not as causative agents of HUS but as contributors that may unmask the condition. The exclusion of a secondary form of TMA is a critical component of the diagnostic process and should be conducted based on clinical presentation and a series of specific laboratory tests [38,39]. Therefore, it is necessary to define the form of HUS (secondary or atypical), bearing in

Table 1
Final consensus statements on the management of atypical hemolytic uremic syndrome (aHUS). Statements in italics were revised between the first and second rounds. Level of consensus was expressed as the proportion of the faculty who scored the statement as 4 (agree) or 5 (strongly agree).

No.	Statement	Level of consensus, %[a]	
		First round (n = 25)	Second round (n = 14)
Section 1: Definition of aHUS			
1	aHUS is a rare, systemic, life-threatening TMA disease characterized by non-immune hemolytic anemia, thrombocytopenia and renal involvement.	100	100
2	aHUS is a multifactorial disease combining genetic or acquired (autoantibodies) abnormalities in the CAP and a triggering background. In adults with aHUS, gene variants appear more commonly than autoantibodies.	96	93
Section 2: Diagnosis			
3	*The diagnosis of aHUS is based on clinical presentation, laboratory criteria and the exclusion of other TMAs. It is characterized by the combination of platelet consumption (platelets < 150,000/mmc or a 25 % reduction from the initial value), microangiopathic hemolysis (hemolytic anemia with negative direct Coombs test, elevated levels of LDH, reduced levels of haptoglobin, with or without the presence of schistocytes in the peripheral blood smear), as well as renal involvement (presence of hematuria and/or proteinuria and/or elevated creatinine)*[b].	92	100
4	*In almost 50 % of cases, not all three main clinical signs (hemolytic anemia, thrombocytopenia and renal involvement) are clearly present at onset*[c].	84	100
5	In the presence of non-immune hemolytic anemia, thrombocytopenia, and renal involvement, it is mandatory to distinguish between typical HUS, atypical HUS, and TTP. In this regard, the enzymatic activity of ADAMTS13 and the presence of VTEC in the stool should be assessed.	100	100
6	*If evidence of non-immune (negative direct Coombs test) microangiopathic hemolytic anemia, ADAMTS13 result should be performed within a few hours as an urgent test*[d].	88	100
7	In case of suspect of neurological involvement in aHUS, a neurological consultation followed by EEG and brain MRI is advisable.	92	100
8	*In pediatric patients, both aHUS and STEC-HUS may appear with bloody diarrhea. A short period of diarrhea or the concomitant appearance of diarrhea and HUS should raise the suspicion for aHUS versus STEC-HUS, as the latter usually appears at the end of the gastrointestinal illness (4–5 days from diarrhea onset)*[e].	72	100
9	*Complement-mediated aHUS can occur at any age, therefore age is not a predictor of aHUS*[f].	80	100
10	Mutations in complement-unrelated genes (e.g., *DGKE, WT1*) should be considered when the disease presents early, typically within the first 12 months of life.	92	100
11	Metabolism-associated HUS is an ultra-rare disease caused by inborn errors in cobalamin metabolism. Despite its rarity, these diagnoses are important to make because they have specific therapies.	100	100
12	A percentage of schistocytes above 1 % is a robust cytomorphological indicator for the diagnosis of TMA in adults.	80	93
13	LDH, haptoglobin and indirect bilirubin levels should be available in Emergency Department and performed in any case of anemia plus thrombocytopenia.	92	100
14	No available laboratory test is sufficiently sensitive, specific, and reproducible to allow for early diagnosis of aHUS relapses. The clinician can rely on the combined use of the:		
14. 1	patient's clinical presentation;	96	100
14. 2	presence of laboratory data suggestive of hemolysis;	100	100
14. 3	appearance/increase of glomerular proteinuria;	84	93
14. 4	appearance of microhematuria;	92	93
14. 5	H-MEC test[g].	60 *	29 *
Section 3: Symptoms and laboratory data			
15	In the event of the development of TMA in the course of autoimmune diseases (such as lupus, antiphospholipid antibody syndrome, etc.), use of medications, malignant hypertension and/or other renal diseases, there may still be an alteration of the complement system; therefore, the diagnosis of aHUS cannot be ruled out.	88	100
16	Common neurological manifestations occurring in aHUS include seizures, vision loss, focal motor deficit, headache, generalized weakness, altered consciousness, hallucinations and, encephalopathy.	100	100
17	Brain MRI findings occurring in aHUS are suggestive of TMA: on FLAIR and T2 sequences, bilateral and symmetrical hyperintensities of the basal ganglia, cerebral peduncles, caudate nuclei, putamen, thalami, hippocampi, insulae and possibly brainstem.	76	93
18	In the post-transplant setting, the absence of marked thrombocytopenia or significant anemia does not exclude a TMA diagnosis.	80	93
19	In the post-transplant setting, using mTOR and/or calcineurin inhibitors may cause TMA. These drugs often act as triggers for aHUS through different mechanisms.	84	93
20	The first level examinations should include:		
20. 1	complete blood count (for hemoglobin and platelet values);	100	100
20. 2	reticulocytes (to assess whether erythropoiesis is increased);	84	93
20. 3	LDH, total and indirect bilirubin, haptoglobin (indicators of hemolysis);	100	100
20. 4	urine physical-chemical examination and microscopic examination of the urine sediment (to assess whether there is hematuria and/or proteinuria and/or cylinders);	100	100
20. 5	creatinine (to assess if renal insufficiency is present);	100	100
20. 6	hemogas analysis[h];	72	71
20. 7	peripheral blood smear (to assess the presence of schistocytes),	100	100
20. 8	coagulation test (INR, PTT, fibrinogen).	80	93
20. 9	*ANA*[i]	48 *	Moved
21	Among the second level laboratory tests, it is necessary to evaluate:		
21. 1	*direct Coombs test (to detect the presence of red blood cell antibodies);*	96	100
21. 2	ANA, anti-ENA, ds-DNA, anti-cardiolipin IgG and IgM, anti-beta 2 GP1 IgG and IgM, LAC (to identify the presence of underlying autoimmune diseases), c-ANCA and p-ANCA	100	93
21. 3	anti-platelet antibodies;	68 *	71
21. 4	C3 and C4 (to identify complement consumption);	92	100
21. 5	proteinuria following 24-hour urine (to assess the extent);	96	100
21. 6	ADAMTS13 assay;	96	100
21. 7	VTEC-STEC;	100	100
21. 8	the urinary antigen of *Streptococcus pneumoniae*;	80	100

(*continued on next page*)

Table 1 (*continued*)

No.	Statement	Level of consensus, %[a]	
		First round (n = 25)	Second round (n = 14)
21. 9	cobalamin and folate.	96	100
Section 4: Prevention			
22	All aHUS should be vaccinated against encapsulated organisms as soon as possible.	92	100
23	*The activated terminal CAP is required for efficient serum bactericidal activity against encapsulated bacteria, including Neisseria meningitidis. Anti-C5 inhibitor treatment increases the risk of invasive meningococcal disease. For this reason, patients receiving anti-C5 inhibitor treatment should receive a quadrivalent A, C, W, Y meningococcal conjugate vaccine and B meningococcal vaccine, as well as at least 2 weeks of antimicrobial prophylaxis with penicillin (or macrolides for penicillin-allergic patients)*[k].	80	100
24	A lack of vaccination against encapsulated bacteria does not hinder the timely administration of anti-C5. In such cases, the patient should receive appropriate antibiotic prophylaxis until adequate vaccination coverage is achieved.	96	100
Section 5: Treatment			
25	*Initiating appropriate treatment within 4–8 hours from diagnosis is highly recommended, as delays are associated with increased morbidity and mortality*[l].	92	93
26	Early administration of eculizumab or ravulizumab (within 7 days) at the onset of the disease enhances hematological and renal outcomes.	96	100
27	*Eculizumab and ravulizumab have the same efficacy in terms of endpoints, but ravulizumab has a more favourable profile in relation to duration of effects, infusion frequency and costs in the maintenance phase*[m].	79	100
28	*Eculizumab/ravulizumab discontinuation in patients with aHUS is not without risk, potentially leading to aHUS recurrence and renal failure. A thorough assessment of risk factors prior to the decision to discontinue eculizumab/ravulizumab is essential*[n].	96	100
29	The new anti-C5 monoclonal antibody (ravulizumab) is administered every 8 weeks (every 4 weeks in pediatric patients weighing<20 kg), improving the quality of life and preserving vascular access in pediatric patients.	96	100
30	There are no randomized trials evaluating the efficacy of anti-complement therapy in aHUS, but those treated with terminal complement blockade (eculizumab or ravulizumab) have an improved prognosis over historical controls, with a significant lower rate of progression to end-stage kidney disease.	91	100
31	In the case of severe non-immune microangiopathic hemolytic anemia, plasma-exchange should be started as soon as possible (12 hours) while waiting for the ADAMTS13 test result.	79	93
32	C5 inhibitors have beneficial effects in resolving TMA in women with aHUS triggered by pregnancy.	91	100
33	The prophylactic use of plasma exchange in combination with rituximab reduces the risk of aHUS relapse in patients with high anti-CFH antibody levels.	82	93
Section 6: Patient management			
34	RD centers identified as of expertise for aHUS should guarantee:		
34. 1	*genetic diagnosis and counselling*[o]*;*	96	93
34. 2	treatment plan;	92	100
34. 3	providing consultancy to the hospitals;	87	100
34. 4	*providing training to the hospitals*[p].	Not drafted	100
35	Patients with particularly severe, life-threatening conditions can be quickly referred to a Centre of reference using a diagnostic decision support system.	96	100
36	Contributing to the harmonization of data collection between different care settings and regional Centers of reference may allow the refinement of workflows and improve outcomes in patients with aHUS.	100	100
37	Genetic investigations must be entrusted to laboratories that guarantee results in 45 days.	79	93
38	The patient on dialysis diagnosed with aHUS can be transplanted without or with a low risk of recurrence thanks to the therapies available today.	83	100
39	Patients on the transplant list without a precise diagnosis must be re-evaluated.	83	100
40	Any lengthening of the interval administration of the inhibitor drug requires monitoring of parameters that control complement activity (i.e., C3, C4, CH50, AP50).	87	93
41	Patients with a diagnostic suspicion of aHUS should be promptly referred to a Centre of reference for the disease to perform diagnostic tests to confirm the diagnosis, minimize any diagnostic delay, and have prompt access to available treatments.	92	100
42	Patients with a confirmed aHUS diagnosis should be informed about the possible genetic transmission of the condition. They should have access to genetic counselling performed by geneticists operating in the RD care network.	100	100
43	In case of critically ill patients with a suspected or confirmed aHUS admitted to ICU in hospitals that are not Centers of reference for the diseases, close collaboration with colleagues working in those Centers is highly recommended for the optimal diagnostic and therapeutic management, also through teleconsultation activities.	96	100
44	Rare diseases registries with a sufficient catchment area and monitoring period can offer valuable insight into the epidemiology of aHUS and patient outcomes and provide data on the real-world use of available treatments.	92	93
Section 7: Awareness			
45	*Considering that patients with aHUS are often pediatric, it is important to create a MDT that includes a neurologist, emergency physician, psychologist, pediatrician, hematologist, family pediatrician, and nephrologist in the area in order to involve not only the patient but also the family*[q].	92	100
46	A multidisciplinary approach is necessary since many patients may be admitted to the ICU at presentation with a suspected diagnosis. This condition should be treated as a medical emergency, and initial supportive measures should be urgently introduced.	100	100
47	For optimal patient outcomes, early recognition, appropriate treatment and a multidisciplinary approach are critical to reduce the risk of irreversible organ damage or death.	100	100
48	Centers of reference for aHUS should have a multidisciplinary composition, including the following core competencies: hematological, nephrological, internist, and transfusion medicine, and should have genetic and laboratory facilities able to guarantee the diagnostic pathway and offer care for both pediatric and adult patients.	96	100

(*continued on next page*)

Table 1 (*continued*)

No.	Statement	Level of consensus, %[a]	
		First round (n = 25)	Second round (n = 14)
49	The interaction among different health professionals supporting the patient diagnostic and therapeutic journey should be promoted, especially if this journey occurs across different networks and settings to avoid or minimize care fragmentation.	100	100
50	Centers of reference should be subject to continuous monitoring performed by the competent regional coordinating Centers evaluating the number of patients diagnosed and cared for and the availability of appropriate diagnostic and therapeutic facilities.	100	100
51	There must be an improvement in intra-societal awareness and education involving emergency medical services and emergency room doctors for early recognition of cases (identify red flags on which to base early diagnostic suspicion).	100	100

[j] In Round 1, this statement read: "direct and indirect Coombs test (to detect the presence of red blood cell antibodies). "

*Median score= 3; median score was ≥ 4 in all the other cases.

ANA, anti-nuclear antibodies; AP50, 50 % alternative pathway; C3, component 3; C4, component 4; C5, component 5; c-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; CAP, complement alternative pathway; CFH, complement factor H; CH50; 50 % hemolytic complement; DGKE, diacylglycerol kinase epsilon; ds-DNA; double-stranded DNA; EEG, electroencephalogram; ENA, extractable nuclear antigen; FLAIR, fluid-attenuated inversion recovery; GP1, glycoprotein 1; H-MEC, human microvascular endothelial cells; HUS, hemolytic uremic syndrome; ICU, intensive care unit; Ig, immunoglobulin; INR, international normalized ratio; LAC, Lupus anticoagulant; LDH, lactate dehydrogenase; MDT, multidisciplinary team; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PTT, partial thromboplastin time; RD, rare disease; STEC-HUS, Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VTEC, verocytotoxin-producing *Escherichia coli*.

[a] Consensus was considered to be met if ≥ 70.0 % (rounded off to the nearest whole percentage) of the panel indicated that they either 'agreed' or 'strongly agreed' with the statement.

[b] In Round 1, this statement read: "The diagnosis of aHUS is based on clinical presentation, laboratory criteria, and exclusion of other thrombotic microangiopathies. It is characterized by the combination of platelet consumption (platelets <150,000/mmc or a 25 % reduction from the initial value), microangiopathic hemolysis (hemolytic anemia with negative direct and indirect Coombs tests, elevated levels of LDH, reduced levels of haptoglobin, and the presence of schistocytes in peripheral blood smear), as well as renal involvement (elevated creatinine, and the presence of hematuria and/or proteinuria). "

[c] In Round 1, this statement read: "In almost 50 % of cases at onset, not all three clinical signs (hemolytic anemia, thrombocytopenia, renal involvement) are clearly present. "

[d] In Round 1, this statement read: "If evidence of non-immune (negative direct Coombs test) microangiopathic hemolytic anemia, ADAMT's 13 result should be available in few hours as urgent test".

[e] In Round 1, this statement read: "In pediatric patients, both aHUS and Shiga toxin-producing Escherichia coli-associated hemolytic uremic syndrome (STEC-HUS) may appear with diarrhea. A short period of diarrhea or the concomitant appearance of diarrhea and HUS should raise the suspicion for aHUS versus STEC-HUS, as the latter usually appears at the end of the gastrointestinal illness (4–5 days from diarrhea onset). "

[f] In Round 1, this statement read: "Complement-mediated aHUS can occur at any age, but its onset is more frequent in childhood, accounting for approximately 10 % of cases in children. "

[g] The statement did not gain consensus in any round because some participants felt that HMEC examination did not have sufficient sensitivity and therefore should not be included in examinations to be routinely performed.

[h] In Round 1, this statement read: "hemogasanalysis (to assess the presence of acidosis). "

[i] In Round 1, this statement was considered a first level test, but it was decided to move ANA to the section on second level tests (consensus statement 21)

[k] In Round 1, this statement read: "The activated terminal complement pathway is required for efficient serum bactericidal activity against encapsulated bacteria, including Neisseria meningitidis. Thus, Eculizumab treatment increases the risk of invasive meningococcal disease. For this reason, patients receiving Eculizumab should receive a quadrivalent A, C, W, Y meningococcal conjugate vaccine and B meningococcal vaccine, as well as long-term antimicrobial prophylaxis with penicillin (or macrolides for penicillin-allergic patients) for the duration of Eculizumab treatment. "

[l] In Round 1, this statement read: "Initiating appropriate treatment within 4–8 hours from diagnosis is essential, as delays are associated with increased morbidity and mortality. "

[m] In Round 1, this statement read: "Eculizumab and Ravulizumab have the same efficacy in terms of endpoints, but Ravulizumab has a more favourable profile in relation to duration of effects, infusion frequency and costs. "

[n] In Round 1, this statement read: "Eculizumab discontinuation in patients with aHUS is not without risk, potentially leading to aHUS recurrence and renal failure. A thorough assessment of risk factors prior to the decision to discontinue Eculizumab is essential. "

[o] In Round 1, this statement read: "the genetic diagnosis of aHUS. "

[p] Statement not drafted in Round 1

[q] In Round 1, this statement read: "Considering that patients with aHUS are often pediatric, it is important to create a MDT that includes a psychologist, pediatrician, hematologist, family pediatrician, and nephrologist in the area in order to involve not only the patient but also the family.

mind that the symptomatology at the onset of the disease can often be confusing [40]. Moreover, aHUS also includes some ultrarare forms, such as mutations of non-complement genes (WT1, diacylglycerol kinase epsilon [DGKE]) or without a defined genetic or autoimmune background. The absence of mutations or known antibodies cannot exclude the involvement of CAP dysregulation.

Defining aHUS correctly is critical because, as an acute, rare, life-threatening disease, frontline healthcare providers need to be able to identify patients promptly and initiate the correct therapy [7].

3.2. Diagnosis

aHUS is diagnosed based on clinical features, laboratory criteria, and exclusion of other TMAs, such as TTP and other forms of HUS. Other authors have attempted to distinguish between different forms of HUS and aHUS as follows: (i) HUS with coexisting diseases or conditions (related to the use of certain drugs, presence of malignant hypertension, or autoimmune diseases); (ii) infection-induced HUS (including Shiga toxin-producing *Escherichia coli* (STEC), *Streptococcus pneumoniae*-induced HUS [41], and HUS induced by pathogens such as influenza A, H1N1, and HIV); (iii) cobalamin C defect-HUS (a very rare form) [42], and (iv) aHUS, which is divided into HUS with dysregulation of the CAP (genetic mutations, immunologic forms), DGKE-HUS and HUS where there is neither an identifiable genetic nor an immunologic cause [7, 43–46]. Alteration of the CAP system can occur when TMA develops due to precipitating factors such as autoimmune diseases (e.g., systemic lupus erythematosus, antiphospholipid syndrome, etc.), during the use of medications, in the presence of malignant hypertension, and/or in the presence of other renal diseases [47–51]. In these scenarios, the diagnosis of aHUS cannot be ruled out (consensus statement 15).

Factors that trigger aHUS may include certain medications, pregnancy, the presence of malignant lesions, infections, and/or organ transplantation; these factors vary and can be confusing at the diagnostic stage, as previously described [36,52,53]. HUS that is directly induced by H1N1, influenza A, HIV, and more recently SARS-CoV2 can also be responsible for rare cases of complement-mediated aHUS and may act as a triggering background factor in some predisposed individuals [54].

aHUS may be difficult to diagnose because all three clinical signs (hemolytic anemia, thrombocytopenia, renal involvement) may not always be clearly present at onset [7]. Moreover, in order to make a correct differential diagnosis in the newborn patient, it is necessary to consider that aHUS may be present even if one of these three parameters are absent: (i) thrombocytopenia, (ii) anemia, and (iii) increased creatinine levels [53]. When determining renal involvement in pediatric patients, creatinine levels should be assessed in relation to age [55].

It is important to note that although no available laboratory test is sufficiently sensitive, specific, and reproducible to allow for the early diagnosis of aHUS relapses, the clinician can rely on the combined use of: (i) the patient's clinical presentation; (ii) the presence of laboratory data suggestive of hemolysis; (iii) the appearance/increase of glomerular proteinuria; and (iv) the appearance of microhematuria (consensus statement 14) [56–58]. The Human Microvascular Endothelial Cells (H-MEC) test was excluded as a test to be routinely performed because it has yet to be standardized, lacks ease of reproducibility, and is not cost-effective.

3.2.1. Genetic factors

In addition to being a multifactorial disease with environmental triggers, aHUS can have a genetic cause [1,43]. Although variants in CAP proteins have been detected in 60 % of cases, there was no identifiable mutation or immunologic background detected in more than 40–50 % [3,59]. Mutations may also occur in coagulation proteins and enzymes that affect the coagulation cascade indirectly; however, it is important to note that aHUS can still be diagnosed when identifiable mutations are not present [3]. Gene variants appear more commonly than autoantibodies in adults with aHUS (consensus statement 2) [9].

Genetic testing is carried out through (1) next generation sequencing of the following genes: complement factor H (*CFH*), *CFHR1–5, C3, CD46, CFI, THBD, DGKE*, and *CFB*; and multiplex ligation-dependent probe amplification of the genes: *CFH, CFHR1, CFHR2, CFHR3, CFHR4*, and *CFHR5*. Once diagnosis is confirmed, the patient should be informed about the possible genetic transmission of the condition [60], and they should have access to genetic counselling performed by geneticists operating in the RD care network (consensus statement 42).

3.2.2. Transplantation

Renal transplantation may trigger aHUS, either as a recurrent episode of the disease or as a *de novo* disease in the renal graft [61]. The clinical scenario is more complicated in recipients of renal transplants than in other individuals, which makes diagnosis of aHUS difficult [1]. Critical issues complicating a correct diagnosis of aHUS in transplant recipients include: (i) need for in-depth knowledge of the pathology; (ii) inability to immediately detect pathology (13 % of patients do not show a significant reduction in platelet count and 38 % of patients with TMA in the post-transplant phase do not exhibit significant anemia or thrombocytopenia); (iii) heterogeneous clinical aspects; (iv) long reporting times, and; (v) the need to 'study' individuals with aHUS within the same household, to detect other possible cases at an early stage [1,62]. Furthermore, there is currently no guideline for the diagnosis of aHUS in patients who have undergone renal transplants. Considering the above, consensus was reached that following a renal transplant, the absence of marked thrombocytopenia or significant anemia should not exclude a TMA diagnosis (consensus statement 18).

Given the therapeutic options available today, patients on dialysis who are diagnosed with aHUS can undergo a renal transplant with a low risk of recurrence (consensus statement 38) [50]. To reduce the risk of aHUS in the case of patients with high anti-CFH antibody levels, plasma exchange in combination with rituximab can be evaluated prophylactically (consensus statement 33); plasma exchange in combination with rituximab has also been suggested in cases where anti-C5 antibody therapy has been discontinued, is not feasible, or when there is no benefit derived with plasma exchange alone [61,63,64].

Some medications used in the post-transplant setting (e.g., mammalian target of rapamycin [mTOR] inhibitors and/or calcineurin inhibitors) can cause TMA and may act as a trigger for the development of aHUS via different mechanisms, such as vascular endothelial growth factor (VEGF) reduction leading to endothelial dysfunction, increased sheer stress, activation of CAP (either directly or indirectly), and/or platelet activation (consensus statement 19) [65–68].

An even more delicate and challenging diagnostic setting is TMA associated with hematopoietic stem cell transplantation (HSCT), which is burdened by a very high rate of morbidity and mortality [69]. The diagnosis is complicated markedly by the concurrent hematological condition. Consequently, a recent consensus paper developed by a group of international experts specifically addressed TMA in this setting, elucidating the diagnostic criteria and risk stratification based on 4 key concepts: (1) diagnosis of transplant-associated TMA (TA-TMA) using clinical and laboratory criteria, kidney tissue biopsy, or gastrointestinal tissue (biopsy is not required); (2) proposed diagnostic criteria using the modified Jodele criteria with additional definitions for anemia and thrombocytopenia; TA-TMA is diagnosed when ≥ 4 of the following 7 features occur twice within 14 days: (i) anemia, defined as failure to achieve transfusion independence despite neutrophil engraftment, with hemoglobin decline by ≥ 1 g/dL or new-onset transfusion dependence; (ii) thrombocytopenia, defined as failure to achieve platelet engraftment, higher-than-expected transfusion needs, refractory to platelet transfusions or ≥ 50 % reduction in baseline platelet count after full platelet engraftment; (iii) lactate dehydrogenase (LDH) exceeding the upper limit of normal (ULN); (iv) schistocytes; (v) hypertension; (vi) soluble C5b-9 (sC5b-9) exceeding the ULN; and (vii) proteinuria ($\geq$1 mg/mg random urine protein-to-creatinine ratio [rUPCR]); (3) increased risk of non-relapse mortality and should be stratified as high-risk TA-TMA if there is presence of: (i) elevated sC5b-9, (ii) LDH ≥ 2 times the ULN, (iii) rUPCR ≥ 1 mg/mg, (iv) multiorgan dysfunction, (v) concurrent grade II-IV acute graft-versus-host disease, or (vi) bacterial or viral infection; and (4) weekly screening for TA-TMA of all allogeneic and pediatric autologous HSCT recipients with neuroblastoma during the first 100 days post-transplant. If there is a diagnosis of TA-TMA, patients should be risk-stratified. If high-risk, the patient should be presented with an opportunity to participate in an available clinical trial for TA-TMA-directed therapy [69].

3.2.3. aHUS in children

The initial episode of complement-mediated aHUS can occur at any age, therefore age is not a predictor of the disease (consensus statement 9) [11]. However, higher rates of mortality occur in children than in adults with aHUS, and prognosis strongly depends on genetic background [8,70].

When aHUS presents in the first year of life, mutations in complement-unrelated genes (i.e., *DGKE, WT1*) should be considered (consensus statement 10) [71]. Inborn errors in cobalamin metabolism can cause an ultra-rare metabolism-associated HUS called methylmalonic acidemia with homocystinuria *cblC type* (*MMACHC;* ORPHA:79282*)*, which eventuates in a cobalamin deficiency (consensus statement 11) [23].

Bloody diarrhea that is caused by STEC in children, may develop into STEC-HUS [23,72]. If the patient presents with a short period of diarrhea or the concomitant appearance of diarrhea and HUS, suspicion for aHUS versus STEC-HUS should be raised, as STEC-HUS usually appears 4–5 days from the onset of diarrhea (consensus statement 8) [72].

4. Symptoms and laboratory data

The presentation of any case of anemia plus thrombocytopenia in the hospital emergency medicine setting should always prompt the determination of haptoglobin, indirect bilirubin, and LDH levels (consensus statement 13) [19,73]. These laboratory data are required because aHUS is characterized by the combination of platelet consumption (leading to blood platelet levels of <150,000/mmc or a 25 % reduction in platelet levels), microangiopathic hemolysis (non-immune hemolytic anemia confirmed with a negative direct Coombs test result, elevated LDH levels, reduced haptoglobin levels, with or without the presence of schistocytes in a peripheral blood smear), as well as renal involvement (presence of hematuria and/or proteinuria and/or elevated creatinine levels) (consensus statement 3).

When the triad of non-immune hemolytic anemia, thrombocytopenia, and renal involvement is present, it is compulsory to distinguish between secondary HUS, aHUS, and TTP. In this instance, it is essential to determine the A Disintegrin and Metalloproteinase with Thrombospondin motifs von-Willebrand Factor proteinase (ADAMTS13) activity (severely deficient, measuring <10 IU/dL in TTP), and the presence of verocytotoxin-producing *Escherichia coli* (VTEC) in the stool (consensus statement 5) [21]. Importantly, testing of ADAMTS13 activity should be conducted urgently if there is evidence of TMA (consensus statement 6).

Although neurological involvement is uncommon in aHUS (occurring in 10–20 % of patients) [20], if suspected, a neurological consultation followed by an electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) scan is advisable (consensus statement 7). This suspicion may be based on the presence of common known neurological manifestations in aHUS, such as neurological symptoms, motor symptoms, generalized weakness, vision changes, seizures, and encephalopathy (consensus statement 16) [20]. Bilateral and symmetrical hyperintensities of the basal ganglia that are observed in fluid attenuated inversion recovery (FLAIR) and T2-weighted sequences in brain MRI scans are suggestive of TMA, possibly due to HUS; other areas of the brain that can be involved in the neurological aspects of aHUS include the cerebral peduncles, caudate nuclei, putamen, thalami, hippocampi, insulae, and possibly, the brainstem (consensus statement 17) [74].

While the presence of schistocytes > 1 % is a robust cytomorphological threshold that favors a diagnosis of TMA in the absence of additional features, the absence of schistocytes should not exclude an earlier diagnosis of TMA (consensus statement 12), due to the low sensitivity of the test for schistocytes [75].

Consensus was sought on two levels of laboratory tests, first-level (consensus statement 20) and second-level (consensus statement 21), to diagnose aHUS. Anti-nuclear antibody (ANA) testing was initially considered to be a first-level test in the first round of voting but was moved to the list of second-level laboratory tests after the second round of voting, because ANAs are not associated with a primary form of aHUS. Although the inclusion of the H-MEC test is not recommended (did not reach consensus threshold in either round of voting), this test may be conducted to aid the diagnosis of an aHUS relapse (see Diagnosis section). First- and second-level genetic tests and immunologic diagnostic, microhematuria, and proteinuria tests should also be performed [24].

5. Prevention of infectious complications

The response to Serogroup B meningococci vaccination was reported to be hampered by immunosuppression [76,77], thus, it is recommended that all patients with aHUS should be vaccinated against pathogenic organisms as soon as possible (consensus statement 22) [78–80].

An activated terminal CAP is required for efficient serum bactericidal activity against organisms such as *Neisseria meningitidis* [81]. Since anti-C5 treatment (eculizumab, ravulizumab) blocks the CAP, the risk of invasive meningococcal disease increases. Consequently, patients receiving anti-C5 treatment should receive a quadrivalent A, C, W, Y meningococcal conjugate vaccine and a B meningococcal vaccine 14 days before or at the start of anti-C5 treatment, or if anti-C5 treatment is initiated as a matter of urgency. Antimicrobial prophylaxis with penicillin (or macrolides for penicillin-allergic patients) should be started on the same day that eculizumab/ravulizumab treatment is started, and continued up to 14 days after vaccination (consensus statement 23) [81]. However, a lack of vaccination against known bacteria should not hinder the timely administration of C5 inhibitors [82]. In these cases, patients should receive appropriate antibiotic prophylaxis (detailed above) until adequate vaccination coverage is achieved (consensus statement 24). Comprehensive vaccination prophylaxis against encapsulated organisms (such as *Streptococcus pneumoniae* and *Haemophilus influenzae*) could be considered, particularly in severely immunocompromised individuals [83]. Moreover, rare cases of gonococcus infection have been described. Therefore, it is essential to inform patients about the risk of gonococcal infections and implement appropriate prophylactic measures, including the use of barrier protection during sexual activity and regular screenings [83].

Importantly, it is recommended that amplified patient awareness, early care-seeking and rapid treatment of symptoms consistent with meningococcal disease are necessary in all patients receiving eculizumab/ravulizumab treatment, regardless of meningococcal vaccination or antimicrobial prophylaxis status [77,79,80].

6. Treatment of aHUS

Once TMA is diagnosed, it is highly recommended that plasma exchange therapy is initiated as soon as possible (consensus statement 25) [1,84], ideally within 12 hours, while waiting for the ADAMTS13 test result (consensus statement 31), as delays are associated with increased patient morbidity [22].

Eculizumab is administered every week of a 4-week initial phase followed by a 2-weekly maintenance phase [35,79]. Ravulizumab is administered as a loading dose, then 2 weeks later, followed by every 8 weeks (every 4 weeks in pediatric patients weighing ≥10 and <20 kg) [34,80]. These dosing regimens preserve vascular access, reduce the burden of aHUS, and improve quality of life of all patients, even the elderly or those with diminished vascular function after several years of dialysis (consensus statement 29) [15,36,51,85].

Early therapeutic intervention with eculizumab/ravulizumab (within 7 days) at the onset of the disease enhances hematological and renal outcomes (consensus statement 26) [19]. Eculizumab and ravulizumab have similar treatment efficacy, but ravulizumab has longer lasting effects, more convenient infusion frequency in the maintenance phase (every 2 weeks for eculizumab vs every 8 weeks for ravulizumab), and possibly lower costs (consensus statement 27) [32].

Although no randomized trials to date have evaluated the efficacy of anti-complement therapy exclusively in patients with aHUS, the terminal complement blockade of eculizumab and ravulizumab have improved the prognosis over historical controls, with a significantly lower rate of death and progression to end-stage kidney disease (consensus statement 30) [28,86,87].

Women who develop aHUS triggered by pregnancy have also benefitted from C5 inhibitors that were instrumental in resolving TMA (consensus statement 32) [88,89]. When considering long-term therapy, it is necessary to assess the patient on a case-by-case basis, administer treatment for at least 6 months, and discontinue therapy after a minimum of 3 months of stabilized/normalized renal function [79,80,90]. It is important to recognize that patients of Chinese and/or Japanese descent may not respond to C5 inhibitors [91]. Studies have shown that individuals in these groups possess polymorphic variants of the C5 gene (c.2654 G→A, c.2653 C→T) in a heterozygous state, which leads to resistance to anti-C5 mAbs [91].

The following should be reviewed when considering long-term therapy in a patient with aHUS: the disease etiopathology, family history, prior renal allograft, risk of relapse, frequency of relapses, acute

systemic manifestations, and the patient's genetic and immunologic background [45,46,58,90,92,93]. Monitoring of parameters such as C3, C4, CH50 (classical pathway, 50 % hemolytic activity), and AP50 (alternate pathway, 50 % hemolytic activity) that control complement hemolytic activity is useful if the interval of C5 inhibitor administration is extended (consensus statement 40) [58,94,95].

Discontinuing treatment with eculizumab/ravulizumab in patients with aHUS is not without risk, since this may lead to aHUS recurrence and renal failure [96]. On average, the risk of relapse emerging from the various studies is between 10–20 % after discontinuation of eculizumab [28,94]. Nevertheless, patients should be thoroughly assessed for risk factors prior to the decision to discontinue eculizumab/ravulizumab treatment (consensus statement 28) [86,94,97–99]. Overall, close patient monitoring after eculizumab/ravulizumab discontinuation is recommended and if a patient experiences a recurrence of aHUS, the C5 inhibitor retreatment is recommended [57,94,96].

7. Patient management

In Italy, RD reference centers for aHUS should (i) offer genetic testing and counseling, (ii) arrange treatment plans, (iii) consult with hospital teams, and (iv) provide training to the MDT (consensus statement 34) [24,100–102]. If aHUS is suspected, the patient should be transferred to a RD reference center promptly to minimize any diagnostic delay, confirm the diagnosis and start on available treatments (consensus statement 41) [84].

To optimize the management of patients long-term, the faculty members agreed that the results of genetic investigations should be received ideally within a few months (consensus statement 37). If patients are on a kidney transplant waiting list and do not have a precise diagnosis, they should be re-evaluated (consensus statement 39) [103]. Referral of patients with particularly severe, life-threatening symptoms to a RD reference center can be facilitated by using a diagnostic decision support system (consensus statement 35). In the case of critically ill patients with suspected or confirmed aHUS admitted to the intensive care unit (ICU) in hospitals that are not RD reference centers, close collaboration with colleagues (through information technology or teleconsultation) working at these centers is highly recommended for optimal diagnostic and therapeutic management (consensus statement 43) [84,100,104].

National strategies to improve the management of and outcomes for patients with aHUS could potentially include refining institutional workflows by standardizing data collection between different care settings and RD reference centers (consensus statement 36) [105]. RD registries with a sufficient catchment area and monitoring period (consensus statement 44), collecting data on aHUS, could offer valuable insights into its epidemiology and patient outcomes, and provide data on the real-world use of available treatments [10,106].

8. Awareness of aHUS

aHUS should be treated as a medical emergency, and initial supportive measures should be urgently and promptly introduced (consensus statement 46) [26]. Early recognition, appropriate treatment and a multidisciplinary approach are critical to achieving optimal patient outcomes and reducing the risk of irreversible organ damage or death (consensus statement 47) [3]. Interaction between different health professionals supporting the patient's diagnostic and therapeutic journey should be promoted, especially if this journey occurs across different networks and settings, and to avoid or minimize fragmentation of care (consensus statement 49) [25].

Because multiple organ systems are involved in patients with aHUS and ICU care is often required, a MDT that includes an emergency physician, a neurologist, psychologist, hematologist, nephrologist, internist and transfusion medicine specialist is important; in the case of pediatric patients, a pediatrician and/or family pediatrician should also be included in the MDT (consensus statement 45) [24–26]. Members of MDTs at reference centers should also have access to genetic and laboratory facilities to guarantee the diagnostic pathway and offer appropriate care to children and adults with aHUS (consensus statement 48).

Competent regional coordinating centers should monitor RD reference centers regularly by evaluating the number of patients under their care and the availability of appropriate diagnostic and therapeutic facilities (consensus statement 50) [105]. Lastly, there should be an improvement in societal awareness and education involving emergency medical services and emergency room doctors for the early recognition of suspected aHUS (to identify red flags on which to base early diagnostic suspicion); a dedicated DTCP should be designed at a national level, and shared with all stakeholders and policy makers (consensus statement 51) [11,101].

9. Conclusions

Multiple Italian SSs, PAs, and CoReMaRs collaborated to develop 51 consensus statements on the diagnosis and management of aHUS with the aim of improving patient management and outcomes. These statements provide a unified framework for the prompt recognition of aHUS pathology, differential diagnosis of aHUS, referral to RD reference centers, relapse prevention measures, selecting between treatment options, patient management by a MDT and improving the overall awareness of aHUS. Some of these statements may apply to other RDs and clinical areas. Despite the broad scope of the consensus statements, several unmet needs in the management of patients with aHUS were identified, including diagnostic suspicion, rapid genetic investigations, regular review of the centers of expertise list (considering the number of treated patients), permanent clinical referral in treatment centers and widespread expertise among adult and pediatric specialists. In addition, families should be involved in the care of and treatment choices for the patient from the time an aHUS diagnosis is suspected. They should be supported from a psychological point of view, especially in the event of the need for surgery. The on-going collaboration of clinicians with PAs is recommended to provide families with additional support. It is hoped that this standardized framework will form the basis of the "digital ecosystem" concept and the development of possible information technology solutions to assist MDTs involved in the management of patients with aHUS.

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Funding

Medical writing assistance and Open Access was funded by Alexion.

Alexion did not play any role in crafting, reviewing, or refining the guidance statements.

Declaration of Competing Interest

EDS: was an invited speakers at meetings supported by Alexion and AstraZeneca. MP was a speaker at symposia sponsored by Alexion Pharmaceuticals. RG is a member of the advisory board of Bayer and Roche, and a speaker at bureau/educational meetings of Pfizer, SOBI, Takeda and Novo Nordisk. M Man has received research grants, reimbursement for travel, and consulting payments from Stealth BT, Takeda, Sanofi Genzyme, Khondrion, Abliva, Reneo, Zogenix and Precision Biosciences; is supported by the Telethon (GSP16001), the E-Rare project GENOMIT (01GM1920B) and the Italian Ministry of Health (2022B9WY4A); and is part of the European Reference Networks EURO NMD and RND. GS has received speaker/consulting honoraria from Sanofi, TEVA, Daiichi-Sankyo, Eli Lilly and MSD. AMS was a speaker at symposia sponsored by Alexion, Kyowa Kirin and others; fees were received on behalf of the Association. GS: has received speaker/consulting honoraria from Sanofi, TEVA, Daiichi-Sankyo, Eli Lilly, and MSD. LG: has received research grants from Abionix and Sanofi; has received speaker honoraria from Bayer and Werfen; served as consultant for Baxter, Tavere, Astrazeneca, GSK, Novartis, Chinook, Roche, Reate, Nestle, Otsuka, Gilead Science, Bayer, and Vifor Fresenius. ADL has been member of the advisory board or scientific consultancy of Sanofi and Agomab, and a speaker/chairperson at sponsored symposia by Alexion, Biogen and Roche.

M Mazzucato, LS, PC, GC, FDI, SDR, FD, AG, GA, AB, SB, LB, PF, EGF, FF, CL, FM, A Pad, A Pas, GDS, BS, AT, CV and LZ have no interests to declare.

Acknowledgments

We would like to thank Nireshnee Ramchundar, PhD, of Springer Healthcare who wrote the outline and first draft of this manuscript. This medical writing assistance was funded by Alexion. This work has been supported by ERKNet; we thank the following ERKNet-affiliated hospitals: The Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (member of the European Reference Network EuroBlood-Net), Azienda Ospedaliero-Universitaria Policlinico, Bari (Pediatric and Adult Units, member of the European Reference Network ERKNet) and The Italian Ministry of Education and Research: Dipartimenti di Eccellenza Program 2023 –2027 -Dept. of Pathophysiology and Transplantation, University of Milan. The study was partially supported by the Italian Ministry of Health – Bando Ricerca Corrente. The Haemostasis & Thrombosis Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico is member of the European Reference Network on Rare Haematological Diseases EuroBloodNet-Project ID No 101157011. ERN-EuroBloodNet is partly co-funded by the European Union within the framework of the Fourth EU Health Programme. The working group of the Italian Pharmacology Society "Rare Diseases and Orphan Drugs – SIF4RARE" is acknowledged for the assistance during the preparation of consensus statements and discussions.

Author contributions

All the listed authors were members of the faculty and were thus involved in the preparation of the consensus statements. All authors critically reviewed the drafts and approved the final manuscript for submission.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2025.107714.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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