WWW.aHUSALLIANCEACTION.ORG

28 February 2022

aHUS Diagnosis Process: Patients' experience of specialist care and the diagnosis decision.

Authors Len Woodward✉ , Linda Burke and Kamal Shah

All aHUS alliance Global Action, UK.

Abstract

Background.

Atypical Hemolytic Uremic Syndrome, or aHUS, results from uncontrolled regulation of the innate part of the immune system, called Complement, causing endothelial damage which results in a thrombotic microangiopathy (TMA). Diagnosis of aHUS from a spectrum of potential TMAs presents a challenge to health care professionals resulting in misdiagnosis, treatment delay and more harmful outcomes. Clinicians and patients believe that the aHUS diagnosis process could be improved.

Methods

We conducted an online survey of global aHUS patients using a questionnaire which sought patients' experience of their aHUS diagnosis process. In one section of the questionnaire, we asked patients about their experience of entering specialist care up to making the aHUS diagnosis.

Results

We found that most patients reported they were in a serious clinical condition on arrival in specialist care. They were to see their health deteriorate further while awaiting an accurate diagnosis, reaching an overall health state index of 1.4/5 (5 being excellent), a fall of 69% from the 3.8/5 reported before illness began. Patients also reported the longest timeline (mean 295 days gross) was spent in this process sub-step because of very long-term misdiagnoses of some patients. Infants experienced the most rapid diagnosis with a median of 3 days from entering specialist care and 78% were diagnosed by the seventh day. For adults it took longer, with only 37% of patients being diagnosed in 7 days or less. Adults also reported poorer health outcomes. The symptoms and clinical tests reported by patients were indicative of a TMA but were not specific to just aHUS. Patients reported that nephrologists were the most likely to make a rapid diagnosis and have fewer long term misdiagnosed patients.

Conclusion

Patients enter specialist care with diagnosis uncertainty and mostly in a serious clinical condition which deteriorates while they await a correct diagnosis and effective treatment. Children were more likely to be rapidly diagnosed than adults and are more likely to recover to pre-illness health than adults, who, overall, experience less health improvement. Diagnosis timelines of 7 days or less have been achieved for some patients, but more work is needed to explore how it could be done better for all aHUS patients of any age.

Introduction

The primary disease aHUS is due to a disorder in an intrinsic part of the innate immune system called Complement. The disease manifests because of dysfunction of control within the Complement system's alternative pathway regulation. An uncontrolled membrane attack complex begins to damage self-endothelial cells, triggering a micro thrombotic event known as Thrombotic Microangiopathy, or TMA.[1]

TMAs are a group of disorders characterized by microangiopathic hemolytic anaemia, thrombocytopenia and microthrombi leading to ischaemia. Though rare, thrombotic microangiopathies are life-threatening conditions that require urgent management. Presenting symptoms may be nonspecific, but basic laboratory tests reveal a specific constellation of thrombocytopenia and anaemia with red blood cell fragmentation leading to deficient blood supply tissue injury and with evidence of organ impairment.[2] Renal dysfunction in aHUS is generally recognized as a clinical hallmark of the disease.[3]

aHUS is the rarest form of primary TMA,[4] and can occur in, and damage, the smallest blood vessels in vital organs, including the kidney and brain, and which can affect all ages.[5]

Key Points

1. Almost two thirds of aHUS patients were in a serious clinical condition when entering specialist care.

2. Infants were more than twice as likely to be diagnosed rapidly, i.e., in 7 days or less, than adults.

3. Reported symptoms and clinical tests revealed a TMA but were not specific to aHUS .

4. Around 89% of patients reported initially being misdiagnosed with another TMA, mostly TTP, and almost one in three remained undiagnosed or misdiagnosed for more than 31 days

5. Ways for a more inclusive approach to aHUS diagnosis offer an opportunity for diagnosis timeline improvement and better outcomes

aHUS is one of a spectrum of thrombotic microangiopathies that have different underlying genetic or acquired causes and effects including infection, pregnancy, malignancy, autoimmune disease, vaccinations and medications.[6] Secondary TMAs can also induce a temporary Complement dysregulation with an overlap between both scenarios which can make diagnosing each difficult.[7]

A TMA is a rare condition but a medical emergency requiring immediate treatment to avoid irreversible organ damage or death. Although the initial onset of this disease can be abrupt, it may occur progressively in approximately 20% of patients (a matter of weeks or months), with sub-clinical anaemia, fluctuating thrombocytopenia, and conserved renal function, before a problematic flare up.[8] A diagnosis of aHUS must follow in a few hours or days to avoid delaying clinically effective treatment.[9] Late diagnosis or misdiagnosis of an acute aHUS onset can result in a mortality of 8% and with 50%–80% of patients progressing to end-stage renal failure.[10]

It is not known how many aHUS patients there are globally. Estimates of prevalence are imprecise and range from around 2 to 10 per million of the population, depending on region and age. The prevalent number of patients can range between 16,000 and 79,000 worldwide. Similarly, the annual incidence rates for aHUS are unknown, but are estimated at between 0.23 to 1.9 per million of the population.[11] At an incidence rate of 0.5 per million globally there could be around four thousand patients onsetting with aHUS in need of a diagnosis each year.

The single most important event that will determine the successful treatment and resolution of a health problem is a correct diagnosis. Clinical diagnosis is a process that begins when someone recognises ill health symptoms and will include a team of experts working to identify the cause of such symptoms.[12]

Patients have identified an aHUS diagnosis as a problem and believe that the process can be improved and so regard it as a priority for research.[13,14] Increasingly patient advocacy organisations are gathering information from patients themselves about their experience and perception of their disease diagnosis to raise awareness

and inform of unmet needs resulting from incorrectly/untimely treated disease following misdiagnosis and diagnosis delays.[15]

aHUS alliance Global Action, an incorporated charitable organisation for global aHUS patient advocacy, has undertaken a global survey of patients' experience and perception of the aHUS diagnosis process. A report on the reasons for the survey, the method used, and the results of the high-level process measures of timeline, health status and perception has been published.[16] A further report has been published about patients' experience of primary care where no diagnosis of aHUS was reported by patients.[17]

The purpose of this study is to measure and describe patients' experience of the aHUS diagnostic process from entering specialist care to receiving an aHUS diagnosis. From the resulting insights to also examine whether current approaches were meeting all patients' needs, and if not, what could be done about it?

Methods

An online questionnaire, using a SurveyMonkey instrument, was employed to gauge experience and perception of the aHUS diagnosis process. Participants were either patients themselves, or their care giver responding on behalf of the patient. The survey questionnaire was launched on 25 November 2020 and remained open until 19 January 2021. The website page with access to the online questionnaire had 654 views during the time that it was open, yielding 227 participants, i.e., a response rate of 35% from all page views.[18] The characteristics and demographics of the study participants are presented in Appendix A.

The survey instrument included forty-two quantitative and qualitative questions structured around the steps in a clinical diagnosis process model conceptualised by the USA institute of Medicine Committee on Diagnostic Error in Health Care.[19] These included the process steps from first experiencing a health problem, seeking medical advice, escalating to specialist care, developing a working diagnosis, gaining a correct aHUS diagnosis and the resulting treatment given. Our questions and format did not seek personal details of patients, their hospitals, or their treating clinicians. Patients were not asked about any interim treatments received during their care before an aHUS diagnosis. The diagnostic process is rarely linear and can involve several sequences of iterative loops, which to have captured fully would make any questionnaire unwieldly. Our concise questionnaire design, therefore, presents the broader experience succinctly.

A section of the questionnaire focussed on patients' experience of specialist care and receiving an aHUS diagnosis. There were 227 respondents from whom data was gathered and analysed, though not all respondents answered the survey in its entirety and so the number of non-responses to questions are shown where applicable.

With no access to patients' medical records, this study is reliant on recollected self or proxy reporting of timelines and events experienced by patients. Responses to most questions are retrospective and demanding best recall of events experienced and felt by the respondents and bias can result. In such an approach it is likely that some events may not be reported, and timelines may differ.[20] The questionnaire was designed to help participants recall variables such as symptoms, tests, treating physicians and health organisation levels but also allowed free form comments for individual's specific recollections.

Bias may also result from the way in which patients participated in the study.[21] Although participants were unselected volunteers, they were from those who were connected in some way with the organisation and website of the aHUS alliance Global Action, either directly or via international aHUS patient social networks that interface with the website. A high proportion of North American respondents, as well as a higher ratio of female patients, may have participated as a result. The experiences and perceptions of this group of study respondents may be more reflective of the developed world and a female patient viewpoint.

Overall, the age and gender characteristics of patients differ little from expected results derived from the sum of other aHUS Global Registry/ Patient Poll reports. [22,23,24,25] There are more aHUS adults than children; and there are more females with aHUS than males. The gender/age differences are also consistent because there are more boys than girls in the infant age group, whereas in older children there is no gender difference. In adulthood aHUS women are much more prevalent than men.

Results

Sub-process measures

Self-reported clinical condition on arrival in specialist care

Table 1 shows patients' reported clinical condition on entering specialist health care. 143 (62%) patients reported they were in a critical or life-threatening state. A higher proportion of adult patients, 69%, reported these severe conditions than infants, 44%, and to lesser extent older children, 54%.

Table 1 Self- reported clinical condition status on entering specialist (n=227)

	All n=227		Infants n=36		Older children n=42		Adults n=149	
Clinical Condition	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Life threatening	71	31	8	22	8	19	55	37
Critical	71	31	8	22	15	36	48	32
Stable	14	6	5	14	3	7	6	4
Worsening	47	21	12	33	12	29	23	15
Debilitating	19	9	3	8	3	7	13	9
Mild	5	2	-	-	1	2	4	3

Self- declared health status

Table 2 presents details of patients' self-declared health state at the time of an aHUS diagnosis and at the time of participation in the study using a version of the EQ-5D instrument. At the time of diagnosis 224 (99%) patients reported their health status as "Good to Very Poor", which converted to an average health state index of 1.4/ out of a possible 5 (a study index construct*). Older children reported the lowest health state index 1.3/5. By the time patients participated in the study 198 (87%) individuals reported their outcome health status had risen to " Good to Excellent ", which converted to an overall average health state index of 3.4/5. Adults reported the lowest outcome health state index of 3.1/5 compared with infant and older children patients, with both groups reporting a score of 3.8/5. Two (1%) adult patients had died.[16]

Table 2 Patients self-declared health state and index at time of diagnosis and at study participation (n=227)

N=227	At time of diagnosis		At time of study participation	
Health State :	**No.**	**%**	**No**	**%**
Excellent	0	0	25	11
Very Good	3	1	77	34
Good	13	6	96	42
Poor	53	23	23	10
Very Poor	158	70	4	2
Deceased	0	0	2	1
Average Health Index*				
All	1.4		3.4	
Infants (n=36)	1.5		3.8	
Older children (n=42)	1.3		3.8	
Adults (n=149)	1.4		3.1	

*A health status index was constructed from EQ-5D health states reported and scored Excellent = 5, Very good = 4 , Good =3 , Poor= 2 to Very Poor =1 then aggregated and averaged by cohort numbers.

Timelines

Table 3 details the timelines from entering specialist care to being diagnosed with aHUS. 107 (47%) of patients reported that it took up to 7 days to receive an aHUS diagnosis and, 69 (30 %) patients reported it took more than 31 days. The longest diagnosis timeline was 5110 days (nearly 14 years). Outlier diagnosis timelines materially affected the mean result of 295 days (gross), but less so a median performance of 10 days. Excluding the over 365-day outliers the mean and median delay becomes 32 days and 7days respectively. Seventy-eight percent of infants were diagnosed with aHUS in 7 days or less of entering specialist care. Infant timeline experience was superior to that of adults, of whom only 38% were diagnosed as rapidly, and to a lesser extent than older children with 50% experiencing a more rapid diagnosis.

Table 3 Timeline from entering specialist care to being diagnosed with aHUS (n=227)

	All (n=227)		**Infants (n=36)**		**Older children (n=42)**		**Adults (n=149)**	
Days	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
1-3	66	29	22	62	12	29	32	21
4-7	41	18	6	16	9	21	26	17
8-31	51	23	5	13	8	20	38	26
Over 31	69	30	3	9	13	30	53	36
Days	**To diagnosis (gross)**	**To diagnosis (net)***	**To diagnosis (gross)**	**To diagnosis (net)***	**To diagnosis (gross)**	**To diagnosis (net)***	**To diagnosis (gross)**	**To diagnosis (net)***
Mean	295	32	36	16	160	35	396	29
SD	856	62	131	61	459	74	1008	65
Median	10	7	3	3	7	7	14	10
Median range	1-5110	1-365	1-2555	1-365	1-2555	1-365	1-5110	1-365

*excluding undiagnosed/misdiagnosed over 365 days.

Specialist Care Pathway

Care profession specialisms and decision makers

Table 4 shows the professional specialisms involved in patients' initial care and a subsequent aHUS diagnosis decision. Of the 155 patients who were immediately escalated to specialist care, only 122 provided data about their initial care specialist. Thirty-seven percent reported their healthcare being given by nephrologists (no distinction was made between adult and pediatric), 31% multi-disciplinary teams and 17% by haematologists. The remaining 15% of patients were first seen by one of six other specialists.

Nephrologists (40%), multi-disciplinary teams (42%) and haematologists (15%) were reported to subsequently make 97% of the aHUS diagnoses. Patients reported nephrologists as having the best overall diagnosis performance for speed and accuracy, with 59% of their patients being diagnosed in 7 days or less (a median level of 6 days), and with only 8% of misdiagnosed patients taking more than 365 days to have their diagnoses corrected. Whilst all other professions shared a median performance of 14 days, haematologists had a better diagnosis timeline performance at 42%, but multi-disciplinary teams had fewer patients (12%) misdiagnosed for more than 365 days. Patients reported higher continuity of care from oncologists and paediatricians but lower diagnostic achievement levels. Other specialists who provided initial care, rheumatologists, urologists, gastroenterologists and intensivists were not reported by any patient as making an aHUS diagnosis.

Table 4 Specialist care pathway and diagnosis decision timelines.

	Initial Care Pathway*	Diagnosis given by:					
Specialist professions	**%**	**No.**	**%**	**% in <7 days**	**Median Days (gross)**	**% in > 365 days**	**% with care continuity**
Nephrologist	37	88	40	59	6	8	70
Haematologist	17	33	15	42	14	18	42
Paediatrician	7	4	2	25	14	50	75
Oncologist	2	3	1	33	14	33	66
Multi-Disciplinary Team	31	91	42	36	14	12	50
Rheumatologist	2	0	0	-	-	-	-
Urologist	1	0	0	-	-	-	-
Intensivist	1	0	0	-	-	-	-
Gastroenterologist	2	0	0	-	-	-	-
Total	100	219	100	47	10	13	59
No responses	33**	8	-	-	-	-	1

*based on data from 122 of 155 patients immediately referred to specialist care from primary care who responded ** Not percentage but number not responding

Patient reported symptoms and clinical tests

Patient Reported Symptoms

Table 5 shows patient reported symptoms on reaching specialist care. 194 (85%) patients reported failing or failed kidney function. 170 (75%) patients recalled having high blood pressure and 164 (72%) had anaemia along with 153 (67%) with body swelling (oedema). Other serious symptoms which were reported by less than half of patients included breathlessness and heart related issues at 89 (39%) and 64 (28%), respectively. A range of symptoms reported by 10% or fewer patients included 22 reporting nausea and GI issue, 11 recalling bleeding, rash, or bruising symptoms, 11 mentioning neurological symptoms, seizures, mental confusion, headaches, insomnia and hallucinations. 9 recollected liver function problems, and 7 reported fatigue or feeling faint and 1 each with blood sugar and general pain issues.

Patient reported clinical tests

Table 6 presents patient reported clinical tests in specialist care. 215 (95%) patients recalled one or more of clinical tests undertaken. 206 (91%) patients reported having blood tests for platelet levels and 193 (85%) for haemoglobin. 147 (65%) reported having imaging tests and 138 (61%) were assessed for E. coli. 125 (55%) had Complement level tests and 114 (50%) had a kidney biopsy. 102 (45%) had ADAMTS13* tested and 97 (43%) had genetic tests. 18 patients (8%) reported a range of other tests. Twelve participants did not respond to this question.

Table 5 Patient reported symptoms

Symptoms	No.	%
Kidney failing/failed	194	85
Very high blood pressure	170	75
Anaemia	164	72
Body swelling	153	67
Breathlessness	89	39
Heart related issues	64	28
Other	62	27

Table 6 Patient reported Clinical Tests

Tests	No	%
Platelets	206	91
Haemoglobin	193	85
Imaging	147	65
E. coli*	138	61
Complement	125	55
Kidney Biopsy	114	50
ADAMTS 13**	102	45
Genetic	97	43
Other	18	8
No response	12	5

* **E**scherichia coli ** **a** **d**isintegrin **a**nd **m**etalloproteinase with a **t**hrombo**s**pondin type 1 motif, member **13**

Working diagnosis

Conditions considered and alternative diagnoses made

Table 7 shows 24 conditions which 134 patients recalled being considered by their specialist as possible causes of their illness. 182 patients reported having alternative working diagnosis decisions prior to an aHUS diagnosis. 90 patients either could not recall, did not understand, or were not told about other conditions considered, and 45 did not recall any other diagnosis decisions made. An average of three alternative conditions were considered to explain the patient's evident health problem. 212 alternative working diagnoses were made prior to one of aHUS. Most were for the overarching condition TMA, other Primary TMAs (TTP,HUS) or Pregnancy TMAs (Pre-eclampsia/Eclampsia/HELLP). A small number of patients received other working diagnoses including Kidney Disease of Unknown Significance, 5 (2%), Food-poisoning 3 (1%) and Meningitis 2 (1%), and 1 patient for each of malignant hypertension, SLE/Lupus, C3GN, Evans Syndrome, GI. Influenza. Malaria, TBMN, and APS.

Table 7 Other Working diagnoses considered and /or made (excluding aHUS)

	Other Working Diagnoses			
	Considered n=214		Made n=227	
	No.	%	No.	%
Overarching:				
TMA	112	82	49	27
Primary TMAs:				
TTP	137	100	80	44
HUS	114	83	45	25
Secondary TMAs:				
Eclampsia/Pre-eclampsia.	18	13	10	4
HELLP	7	5	5	3
SLE/Lupus	8	6	2	1
APS	2	1	2	1
Malignant Hypertension	0	0	1	0
KFUS	1	0	5	2
TBM Nephropathy	1	0	1	0
Evans Syndrome	0	0	1	0
ITP	3	2	1	0

Table 7 Continued

Triggering or other conditions :	No.	%	No	%
Food poisoning	0	0	3	2
Meningitis	0	0	2	1
Leukaemia	2	1	0	0
Rota Virus	1	0	0	0
C3GN	0	0	1	0
Glomerulonephritis	0	0	1	0
Gastrointestinal	1	0	1	0
EBV	1	0	0	0
Hepatitis	1	0	0	0
HIV	1	0	0	0
Influenza	0	0	1	0
Malaria	0	0	1	0
Total	409		212	
Respondents	137		182	
Did not understand	36		0	
Not told	16		0	
Do not recall	38		45	

TTP, Thrombotic Thrombocytopenic Purpura ; HELLP, Haemolysis Elevated Liver Enzymes and Low Platelets; SLE, Systemic lupus erythematosus ; APS, Antiphospholipid Syndrome ; TBM, Thin Basement Membrane; ITP, Idiopathic Thrombocytopenia Purpura; C3GN, C3 Glomerulonephritis ; EBV, Epstein-Barr virus.; HIV, Human Immunodeficiency virus

Genetic confirmation of diagnosis

In Appendix A the numbers of aHUS diagnoses which were **confirmed** by genetic testing are shown by patient age and gender. One hundred and sixty-eight (74%) patients' aHUS diagnoses were confirmed by a test for predisposing genetic causes. Fifty-eight patients (26%) were either to be found idiopathic after a test or had no genetic test performed. More positive results (87%) were reported by those patients under 18 years. Over 9 out of 10 infants were found to have a genetic predisposition. Fewer adult female patients' diagnoses were confirmed by genetic tests than adult male patients. (64% v 82%).

Discussion

Health state, symptoms, tests and differential diagnostic tools

All patients entered the specialist care pathway from primary care without an aHUS diagnosis, although five patients reported having other suspected TMAs[17]and as previously reported, just over half would immediately enter intensive care.[16] Nearly two thirds of patients described their clinical condition as "critical/life-threatening" on arrival in specialist care (Table 1). All would receive an aHUS diagnosis eventually, but their timelines would vary, and, overall, patients would report spending most time in this step of the diagnosis process.[17]

A TMA is characterised by thrombocytopenia (low or no platelets), haemolysis (destroyed blood cells) and impairment and damage of one or more organs, brain, kidney, GI, heart, lungs or eyes. Whilst only 11 patients reported symptoms of thrombocytopenia (unusual bleeding, bruising), clinical tests by their clinicians for platelets were recalled by almost all patients (Tables 5 and 6). Most patients did, however, describe having symptoms of anaemia and reported that their haemoglobin levels were assessed. These two clinical manifestations plus schistocytes (red blood fragments on blood film) would be sufficient for a suspicion of TMA [2] Participants also reported impairment of two or more organs. Primarily the kidney in 85% of instances and the heart by 20% of patients. There is a possibility of impairment of lungs among the patients reporting

"breathlessness" and brain with neurological symptoms (including seizures and mental confusion) and some liver issues. However, the range of symptoms reported were not specific to aHUS and would likely overlap with other TMAs and that would complicate diagnosis.[26]

Often patients present with a constellation of symptoms, signs, and test data which reveals a pattern of disease with which a clinician is familiar and can make a diagnosis. Sometimes patients present with an illness that does not easily fit a pattern and a differential approach to diagnosis is required.[27] An aHUS diagnosis begins with the broad diagnosis of TMA.[28] The challenge then is about how to make an efficient and accurate differentiating diagnosis among those TMAs[29] to quickly **suspect**, and rapidly **establish**, but not necessarily **confirm,** the cause of the TMA as aHUS before treating it effectively. [10]

According to surveys of clinicians it is claimed that a differential diagnosis of a TMA is made within 1-7 days of presentation in 92% of cases.[30] In Table 3, our study shows that some aHUS patients (47%) report that such a timeline is possible, predominantly for infant patients (78% in 7 days or less), but it is less so for older children (50%) and much less for adults (38%). The surveys referred to did not drill down into the type of TMAs diagnosed so it is not possible to say whether aHUS TMAs might have featured disproportionately in the 8% reporting a "more than 7 day" diagnosis timeline.

Clinically It has been hypothesised that early effective treatment and a younger age are suggestive of less renal damage at treatment initiation, and, therefore, with greater potential for recovery of kidney function; and that renal outcomes are better for patients being treated rapidly (up to 7 days) of an aHUS presentation, than those treated later.[31] We found a disparity between the diagnosis performance for children and adults. Furthermore, we found a disparity also in the self- reported health states at the time of study participation. After diagnosis children returned to pre-illness levels, older children improving slightly by + 0.1/5, and infants falling slightly by -0.1/5 (Table 2). Adults did not report the same degree of recovery following diagnosis and, at time of participation, responded that their health state was 18% less than their pre illness level i.e., down from 3.8/5 to 3.1/5.[16] This is suggestive, depending also on comparative treatments, that the hypothesis has some merit and that aHUS patients are right to claim that diagnosis process performance may not be optimal for all patients to benefit.

For rapid diagnosis of aHUS in the acute setting, the diagnosis process also needs treating physicians to be aware of rare diseases to recognise and manage them through from symptoms and tests to a decision. Patients reported that the better overall diagnosis practice was provided by nephrologists (Table 4). More than two in five patients reported that they considered their diagnosis to be result of a multi-disciplinary team. Our questions did not elicit whether the team working developed on a case-by-case basis because of diagnosis difficulty or was a predetermined team protocol to be invoked when a TMA was suspected. The latter process has been the subject of interest in recent TMA literature claiming benefits of earlier suspicion and identification of manifesting TMAs and improved renal outcomes.[32] Careful extensive workup of TMA is mandatory in patients with TMAs, and it probably requires the education of clinicians and inter disciplinary approaches, including the creation of "TMA Teams".[33] It may bring improvement to a TMA diagnosis process, and a subsequent aHUS Diagnosis Process, if further study is undertaken to establish a possible best practice for TMA Teams.

Only one patient reported intial care by an intensivist despite more than half of patients entering specialist care via Intensive Care Units. The profile and beneficial role that intensivists can play in the early detection of TMAs in the care pathway needs to be elevated. From experience it is estimated that intensivists may see three cases of TMA each year on average and are well placed to make an earlier recognition of manifesting TMAs to invoke an established TMA team protocol.[28] Although no patient directly recalled a pathologist's part in their care, the complexity of TMA pathological findings depend on this specialism for delving further into clinical and laboratory data, particularly where expected features are absent. Renal pathologists also have a key TMA Team role to play.[34]

There is more than one cause of TMA. Each has a different pattern of development and a need to be treated differently. Our questionnaire did not seek the manner of treating physicians' individual clinical reasoning but from the conditions recalled by patients in Table 7, and the subsequent interim working diagnoses decisions, it

suggests differential diagnosis approaches had been deployed. In published TMA literature there are several recommended TMA decision making guidelines for differential diagnosis, within differing clinical contexts and with some in an algorithm format. Table 8 illustrates the disease priorities for five published guidelines.[35,36,37 38,28]

Table 8 Disease priorities in published differential decision making guidelines

Priority	Adults	Children	Pregnancy	Transplant	Intensive Care
1	Secondary TMAs	Co-Existing Disease/Condition HUS	Eclampsia/Pre-eclampsia/ HELLP	ABMR	DIC
2	TTP	S.pneumoniae HUS	TTP	Calcineurin Inhibitors	TTP
3	HUS	Influenza A /H1N1 HUS	Sepsis	Infection	HUS
4	aHUS	Congenital TTP	DIC	TTP/ STEC-HUS	aHUS
5		STEC- HUS	Immune secondary TMAs (Lupus , CAPS)	aHUS	
6		Cobalamin C defect HUS	B9/B12 deficiency		
7		aHUS	Cobalamin C defect TMA		
8			Other secondary TMAs		
9			HUS		
10			aHUS		

HELLP, Haemolysis Elevated Liver Enzymes and Low Platelets; ABMR, Antibody Mediated Rejection; DIC, Disseminated Intravascular Coagulation; TTP, Thrombotic Thrombocytopenic Purpura; STEC, Shiga toxin-producing E. coli, CAPS, Catastrophic Antiphospholipid Syndrome

aHUS has the lowest perceived priority in each guideline despite modifiers for age and triggering contexts. Higher incidence/ clinical severity/ disease specific clinical tests availability place the other primary TMAs, TTP and HUS above aHUS in diagnosis priority. Similarly, all secondary TMAs are usually considered before aHUS. Consequently, aHUS is only suspected when other causes of TMA are ruled out after the time taken to gather their clinical data and for other TMAs to be evaluated. The aHUS diagnosis process has been described as one of exclusion[39] and it can delay administration of effective treatment. Such an approach needs to be communicated effectively to limit anxiety and loss of confidence in patients facing diagnosis uncertainty.[40] Only 137 (60%) patients recalled other conditions being considered and 36 (16%) reported they did not understand what was being considered (Table 7).

In our study 182 patients reported having been misdiagnosed with other primary and/or secondary TMAs before a correct aHUS diagnosis was made, thereby prolonging the time to effective treatment. TTP was the most common misdiagnosis, followed by HUS and pregnancy associated TMAs, pre-eclampsia/eclampsia. Some of the misdiagnoses would remain for years before being corrected. This raises the prospect that there may still be others who remain undetected.

"Inclusive" diagnosis opportunities

Inherent delays in a diagnosis by exclusion may not have made material difference to patients' outcomes in the past when there was no clinically effective Complement inhibitor treatment for aHUS, nor in the present where patients have no affordable access to Complement inhibitors like eculizumab or ravulizumab. Treatment innovations and current understanding of TMAs may incentivise and permit the prospect for more aHUS inclusive diagnosis opportunities to improve outcomes.[41]

Penetrance of aHUS in families is complicated and can be incomplete and has been estimated to be between 20% and 50%.[42 43] Knowledge of a family history of aHUS has been a potential modifier to the differential diagnosis process. Yet even if a family history is known and disclosed to a clinician, it may not alter a diagnosis by exclusion approach.[44] Twenty-one patients reported having a family history of aHUS (Appendix A), 9 of

them found out about their families' history after their diagnosis. Of the twelve patients who knew, four were diagnosed with aHUS within 24 hours of entering specialist care and another one within 7 days. For others it took longer, two were within 31 days and it took two months for another two to be diagnosed. For three patients, it took over five hundred days to be diagnosed, with the longest taking 729 days. For patients discovering a family history long after a misdiagnosed onset, it may have meant their diagnosis could be corrected. There are social and communication barriers to overcome for wider family members to be aware of a potential genetic susceptibility to aHUS. Given the severity of aHUS there may be merit in screening family members for the specific mutation responsible for the disease in their family.[42] Some families have found using an aHUS "alert card" advantageous.[45,46]

There has been no diagnostic test that conclusively confirms aHUS.[47] The lack of a specific and sensitive biomarker for Complement associated TMA puts aHUS patients at a disadvantage in the acute setting. In our study around half of patients recall having tests for Complement levels and/or predisposing genetic variants . Unless done rapidly (within 7 days of any suspicion of aHUS) genetic test results would not help to establish a rapid aHUS diagnosis.[48] There is little public information about test turnaround service levels or fees, but some laboratories offer next generation sequencing (NGS) reports in 4 to 8 weeks and Sanger Sequencing technology in up to 4 weeks.[49,50] Such service levels could be used to **confirm** a diagnosis in the majority of cases [10] and for prognosis and familial predisposition screening awareness. Seventy-eight percent of patients reported that genetic testing **confirmed** their aHUS diagnosis (Appendix A). One laboratory was found to offer a 48-hour turnaround from blood sample receipt to reporting, which could assist a rapid diagnosis.[51]

Testing for Complement component levels C3, C4 etc has not been shown to be a reliable measure of an aHUS onset. Complement activation mediated by the alternative pathway in aHUS would be predicted to result in low levels of C3 and normal C4 levels. Although this has been reported in aHUS patients, additional studies suggest that no more than half of patients diagnosed with aHUS confirmed by mutation studies will demonstrate the expected low C3 and normal C4 levels, limiting their utility in the diagnosis of aHUS.[52] The level of the Complement membrane attack complex, C5b-9, has been seen as a potential marker for Complement activation, and has been used to assess Complement blockage in inhibitor treatment. The value of measuring the level of C5b-9 in blood for diagnosis of aHUS remains unresolved but not entirely dismissed.[53] A test of C5b-9 deposition on endothelial cells, HMEC-1, is believed to have some value and may critically reduce diagnosis timelines.[54] It is not a rapid test and currently has limited availability.[41]

Unless there is a risk of bleeding, a kidney biopsy is regarded as the gold standard for kidney TMA diagnosis [41], although other TMA mimicking conditions can add to the diagnostic dilemma.[55] It is a memorable procedure for aHUS patients and only half of participants reported this test being performed. Results, however, have not been specific to aHUS or Complement. Recently pathological studies of renal injury during TMA episodes may have found a link to Complement disease. The degree of interstitial fibrosis and tubular atrophy (IF/TA) may provide clues on underlying disease mechanisms. A severe and advanced extent of IF/TA supports the notion that a genetic mutation is present and affecting the Complement system. If the extent is minimal or mild it is more likely that autoantibodies targeting Complement regulation are present and not pathogenic mutations.[34]

Uncontrolled Complement has been seen to be implicated in Secondary TMAs as an underlying mechanism for endothelial damage, either wholly, or in part, along with damage caused by those conditions themselves.[47] Another way to differentiate TMAs is by whether the underlying conditions are responsive to plasma exchange therapy and/or Complement inhibitors.[6] aHUS has not been as responsive to plasma exchange as TTP, which would not be as responsive to Complement inhibitors. Increasingly, however, Secondary TMAs are being found to respond to Complement inhibitors, if only as a temporary treatment until the underlying condition is resolved [41] With more understanding an interim Complement inhibitor treatment strategy could be adopted for all patients suspected of having a "Complement TMA".[47] Patients with Secondary TMA conditions could benefit from time limited Complement inhibitor therapy and for undiagnosed aHUS patients treatment would be delivered sooner.[39] Further research is in progress to better categorise TMAs, including pregnancy TMAs, into different groups with potential therapeutic and prognostic implications, including the use of a Complement inhibitor.[56,57,58]

The incidence of TMA per million of the population is not known, nor is the individual incidence of each category of TMA, but the probability of a TMA case presentation being aHUS is very low. In one study of adult TMA incidents in a Region over an eight-year period, the likelihood of a TMA being aHUS was put at 1 in 37, slightly less likely than for the other primary TMA, TTP which was 1 in 30. Most incidents of TMAs were found to be Secondary.[59] Throughout the literature about TMA differential diagnosis there are observations of contrasting organ damage probabilities resulting from the various TMA conditions – "Acute kidney injury is much more likely in aHUS than TTP", "The need for renal support, such as haemodialysis, is not a common feature of TTP", "More TTP patients have neurological involvement that aHUS patients"[27], "aHUS is more likely to happen post-partum".[60] Similarly, differences in the likelihood of specific TMAs have been observed from clinical measures. Collectively these observations may add value to an inclusive diagnosis process.[61] This approach has been taken further in the development of a scoring system for diagnosing aHUS.[62]

As has been seen, differential diagnosis guidelines or algorithms are usually designed with a vertical layout with aHUS usually positioned at the end of the process. Another way of presenting the process is by using a horizontal design with causes of TMA shown at one level and preceded by disease presentation probabilities.[63] A "simultaneous" suspicion view of TMAs offers more visibility for aHUS. The narrowly defined diagnosis of aHUS limits treatment options and is particularly injurious to the patient.[39] The outcome of an aHUS nomenclature review could further enhance TMA diagnostic decision making tools for earlier diagnosis and benefit aHUS patients.[64,65]

A summary of the inclusive diagnostic opportunities is given in Fig 1. Other than for family history, where patients' families can create familial awareness to inform treating clinicians, these opportunities for greater Complement and aHUS disease inclusion depend considerably on research dissemination and education for it to be translated into best clinical practice, a challenge for all.

- Family history and family awareness of, and screening for, aHUS
- More rapid genetic test turnaround including C5b-9 deposition biomarker
- Biopsy IF/TA test
- Investigation of prevalence of Complement over activation in Secondary TMAs
- Interim treatment strategy for Complement TMAs
- Comparative symptom/tests probabilities and scoring index
- Diagnosis decision making models with vertical orientation for all TMAs
- Specifically defined disease nomenclature for TMAs to clarify and direct identification
- TMA Team working protocol

Fig.1 Inclusive Diagnosis Opportunities

Conclusion

Most aHUS patients arrive in specialist care in a severe health condition. Our study has shown that most aHUS patients are not being diagnosed as rapidly as is needed to get the best of outcomes. The presenting symptoms and clinical tests study participants reported overlapped with other TMA patients. Since aHUS can mimic other conditions its diagnosis remains one of exclusion. The priorities of a differential diagnosis process put aHUS patients in an unfavourable position compared with other causes of TMA. Our data has revealed that younger children experience a much better process timeline than adults, and in general, it is adult aHUS patients who experience the worst health state outcomes and are most likely to experience long term misdiagnosis.

Awareness of a family history of aHUS, potential biomarkers tests, probability analysis/scoring methods, greater understanding of Complement's role in Secondary TMAs, easier to understand TMA disease nomenclature and the development of a broader TMA multi-disciplinary team approach have been identified. These offer opportunities to lower the "suspicion bar" for aHUS with a more inclusive consideration within TMA diagnoses, allowing clinicians to identify and treat more aHUS TMAs sooner.

The impact of the diagnosis process experience on patient perception and health outcome needed to be expressed and deserves to be heard. Patients and carers share anecdotes about their lived experience of an

aHUS diagnosis in social media and at aHUS patient gatherings. Amplifying their voices can provide meaningful insight for stakeholders. To the best of our knowledge this is the first study of the aHUS diagnosis process relying on patients' recalled experience, rather than medical records. This study shifts individual anecdotes to a shared perception of health care practice at a very difficult time. Collectively, patients tell what it is like to go through the process to be diagnosed with the rare disease aHUS.

Appendix A Characteristics of patients participating

	Infants		Older children		All under eighteen		All eighteen and over		All patients	
	No .	%	No.	%	No.	%	No,	%	No	%
Age (years) :										
0 to 18	36	16	42	18	78	34	-	-	78	34
18 to 54	-	-	-	-	-	-	127	56	127	56
Fifty-five and over							22	10	22	10
Total	36	16	42	18	78	34	149	66	149	100
Gender:										
Female	16	7	21	9	37	16	119	53	156	69
Male	20	9	20	9	40	18	29	12	69	30
Other	-	-	1	0.5	1	0.5	1	0.5	2	1
Regional territory:										
N. America	20	9	20	9	40	18	103	45	143	63
Europe	6	3	15	7	21	9	37	17	58	26
Rest of World*	10	4	7	3	17	7	9	4	26	11
Lifestyle:										
Infant	36	16	-	-	36	16	-	-	36	16
Studying	-	-	42	18	42	18	21	10	63	28
Working	-	-	-	-	-	-	107	47	107	47
Retired	-	-	-	-	-	-	10	4	10	4
Other**	-	-	-	-	-	-	11	5	11	5
Diagnosed:										
Pre-2011	10	4	8	3	18	7	18	7	36	14
2011-2015	6	3	11	4	17	7	44	21	61	28
Post-2015	20	9	23	11	43	20	87	38	130	58
Family History:										
aHUS known	4	2	1	0.5	5	2.5	7	2.5	12	5
aHUS not known	1	0.5	2	1	3	1.5	6	2.5	9	4
No history	31	13.5	39	16.5	70	30	136	61	206	91
Kidney disease known	6	3	4	2	10	5	30	13	40	18
Kidney disease not known	2	1	2	1	4	2	5	2	9	4
No history	28	12	36	15	64	27	114	51	178	78
Genetic variant * **										
All Yes	32	14	35	15	67	29	101	45	168	74
All No	3	1	7	3	10	5	48	21	58	26
Overall +ve %	91	-	83	-	87	-	68	-	74	
By Gender										
Female -Yes	14	6	16	7	30	13	76	34	106	47
Female- No	1	0.5	5	2	6	2	43	20	49	22
Female +ve %	93	-	71	-	83	-	64	-	68	
Male -Yes	18	8	18	8	36	16	24	10	60	26
Male – No	2	1	2	1	4	2	5	2	9	4
Male +ve %:	90	-	90	-	90	-	82	-	87	
Other Yes	-	-	1	-	1	-	1	-	2	1
Other +ve %	-	-	100	-	100	-	100	-	100	

*Africa-2, Asia-10, Oceania-12, South America-2 ** homemaker-2 ill-2 maternity-5 unemployed-2

*** 1 no response

Acknowledgements.

The authors would like to thank Michael Eygenraam, Margriet Eygenraam, Emma Woodward, Jeff Schmidt, Prof. Anthony Chang, and Dr Anuja Java for their input to the contents of our questionnaire. The help of all patients and family carers who completed the questionnaire is greatly appreciated and gratefully acknowledged.

Authors contributions.

LW, LB, KS conceptualised and designed the study. LW, LB, KS designed the data capture instrument and KS set it up online. LW and KS undertook the analysis and LW drafted the initial version of the manuscript. All authors contributed to the revision of the manuscript. All authors read and approved the final manuscript.

Funding aHUS alliance Global Action

Competing interests. None

Author details 1,2& 3 aHUS alliance Global Action , Knutsford, Cheshire, UK.

References

1 Loirat, C., Frémeaux-Bacchi, V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* **6,** 60 (2011). https://doi.org/10.1186/1750-1172-6-60

2 Arnold, DM., Patriquin CJ., Nazy I. Thrombotic microangiopathies: a general approach to diagnosis and management. *CMAJ*. 2017;189(4):E153-E159. doi:10.1503/cmaj.160142

3 De Yao,J., Kaplan, R,, Magro, C. (2015) An Atypical Case of Atypical Hemolytic Uremic Syndrome: Predominant Gastrointestinal Involvement , Intact Renal Function and C5b-9 Deposition in Colon and Skin. *Journal of Hematology* , 4(3) ,193-195.

4 Nguyen MH., Mathew JJ., Denunzio TM., et al. Diagnosis of atypical hemolytic uremic syndrome and response to eculizumab therapy. *Hawaii J Med Public Health*. 2014;73(9 Suppl 1):22-24.

5 Fremeaux-Bacchi V., Fakhouri F., Garnier A., et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. *Clin J Am Soc Nephrol*. 2013;8(4):554-562. doi:10.2215/CJN.04760512

6 Aigner C., Schmidt A., Gaggl M., et al. An updated classification of thrombotic microangiopathies and treatment of complement gene variant-mediated thrombotic microangiopathy, *Clinical Kidney Journal*, Volume 12, Issue 3, June 2019, Pages 333–337, https://doi.org/10.1093/ckj/sfz040

7 Bernabeu A I., Cavero Escribano T., Cao Vilarino M. Atypical Hemolytic Uremic Syndrome: New Challenges in the Complement Blockage Era. *Nephron* 2020;144:537-549. doi: 10.1159/000508920

8 Franchini M. Atypical hemolytic uremic syndrome: from diagnosis to treatment. *Clin Chem Lab Med*. 2015 Oct;53(11):1679-88. doi: 10.1515/cclm-2015-0024. PMID: 25803082.

9 Campistol JM., Arias M., Ariceta G., et al, An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia*. 2013 Jan 18;33(1):27-45. English, Spanish. doi: 10.3265/Nefrologia.pre2012.Nov.11781. PMID: 23364625.edsr

10 Noris M., Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med*. 2009 Oct 22;361(17):167687. doi: 10.1056/NEJMra0902814. PMID: 19846853

11 Yan K., Desai K., Gullapalli L., et al. Epidemiology of Atypical Hemolytic Uremic Syndrome: A Systematic Literature Review. *Clin Epidemiol*. 2020;12:295-305. Published 2020 Mar 12. doi:10.2147/CLEP.S245642

12 Epstein, H.M., 2019, The most important medical issue ever: And why you need to know more about it. *Dx IQ, No. 1*, The Society to Improve Diagnosis in Medicine.

13 aHUS alliance Global Action, aHUS Global Patients' Research Agenda, Accessed 8/10/2021 *https://www.ahusallianceaction.org/ahus-global-patients-research-agenda/*
14 Woodward, L., Johnson, S., Walle, J.V. *et al.* An innovative and collaborative partnership between patients with rare disease and industry-supported registries: The Global aHUS Registry. *Orphanet J Rare Dis* **11,** 154 (2016). https://doi.org/10.1186/s13023-016-0537-).
15 Daly R., Partovi R., Davidson P. Lupus Diagnosis: Process and Patient Experience [abstract]. *Arthritis Rheumatol.* 2017; 69 (suppl 10). https://acrabstracts.org/abstract/lupus-diagnosis-process-and-patient-experience/. Accessed May 14, 2021.
16 Woodward L., Burke L., and Shah K. Patients' experience and perception of the diagnosis process of the rare disease, atypical Hemolytic Uremic Syndrome, *WWW.aHUSALLIANCE ACTION.ORG.*,2021,https://www.ahusallianceaction.org/wp-content/uploads/2021/09/aHUS-Diagnosis-Process-Patients-Experience-and-Perception-Report-1.pdf Retrieved 7 February 2022
17 Woodward L., Burke L., and Shah K. aHUS Diagnosis Process: patients' experience from first symptoms to escalation into specialist care, *WWW.aHUSALLIANCE ACTION.ORG.*,2021, https://www.ahusallianceaction.org/wp-content/uploads/2021/12/aHUS-Diagnosis-Process-Patients-experience-on-first-seeking-medical-advice-Report-2.pdf Retrieved 7 February 2022
18 aHUS alliance Global Action, *Help needed to join the aHUS dots, https://www.ahusallianceaction.org/help-needed-to-join-the-ahus-dots/* Accessed 7 February 2022
19 Committee on Diagnostic Error in Health Care; Board on Health Care Services; Institute of Medicine; The National Academies of Sciences, Engineering, and Medicine; Balogh EP, Miller BT, Ball JR, editors. Improving Diagnosis in Health Care. Washington (DC): National Academies Press (US); 2015 Dec 29. Available from: https://www.ncbi.nlm.nih.gov/books/NBK338596/?report=reader%20citation doi: 10.17226/21794
20 Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. *J Multidiscip Healthc*. 2016;9:211-217. Published 2016 May 4. doi:10.2147/JMDH.S104807
21 Hess LM, Method MW, Stehman FB Patient Recall of Health Care Events and Time to Diagnose a Suspected Ovarian Cancer, Clinical Ovarian and Other Gynaecologic Cancer, 2012 Volume 5, Issue 1, pages 17-23
22 Licht C, Ardissino G, Ariceta G, et al. The global aHUS registry: methodology and initial patient characteristics. *BMC Nephrol*. 2015;16:207. Published 2015 Dec 10. doi:10.1186/s12882-015-0195-
23 Schaefer F, Ardissino G, Ariceta G, et al. Global aHUS Registry. Clinical and genetic predictors of atypical hemolytic uremic syndrome phenotype and outcome. Kidney Int. 2018 Aug;94(2):408-418. doi: 10.1016/j.kint.2018.02.029. Epub 2018 Jun 19. PMID: 29907460.
24 aHUS alliance Global Action , aHUS *Global Poll 2014- A Commentary on the Data* . 2014, Retrieved 7 February 2022 https://www.ahusallianceaction.org/wp-content/uploads/2019/02/aHUS-Global-Poll-2014.pdf
25 aHUS alliance Global Action, *aHUS Global Poll Results, Q4 & Q5,* 2016. Retrieved 7 February 2022 https://www.ahusallianceaction.org/wp-content/uploads/2016/07/Slide03-1.jpg
26 Barbour T, Johnson S, Cohney S, Hughes P. Thrombotic microangiopathy and associated renal disorders. *Nephrol Dial Transplant*. 2012;27(7):2673-2685. doi:10.1093/ndt/gfs279
27 Saint S, Chopra V : Approach to Differential Diagnosis-The Saint-Chopra Guide to Inpatient Medicine,*OxfordUniversityPress,*PublishedNovember ttps://m.oxfordmedicine.com/mobile/view/10.1093/med/9780190862800.001.0001/med-9780190862800-chapter-1 2018,
28 Azoulay E, Knoebl P, Garnacho-Montero J, et al. Expert Statements on the Standard of Care in Critically Ill Adult Patients with Atypical Hemolytic Uremic Syndrome. *Chest*. 2017 Aug;152(2):424-434. doi: 10.1016/j.chest.2017.03.055. Epub 2017 Apr 23. PMID: 28442312
29 Laurence J, Haller H, Mannucci PM, Nangaku M, Praga M, Rodriguez de Cordoba S. Atypical hemolytic uremic syndrome (aHUS): essential aspects of an accurate diagnosis. *Clin Adv Hematol Oncol*. 2016 Nov;14 Suppl 11(11):2-15. PMID: 27930620.
30 Sakari Jokiranta, T., Viklicky, O., Al Shorafa, S. *et al.* Differential diagnosis of thrombotic microangiopathy in nephrology. *BMC Nephrol* **18,** 324 (2017). https://doi.org/10.1186/s12882-017-0727-y
31 Walle JV, Delmas Y, Ardissino G, Wang J, Kincaid JF, Haller H. Improved renal recovery in patients with atypical hemolytic uremic syndrome following rapid initiation of eculizumab treatment. J

Nephrol. 2017 Feb;30(1):127-134. doi: 10.1007/s40620-016-0288-3. Epub 2016 Mar 19. PMID: 26995002; PMCID: PMC5316393.
32 Uriol R M G, Cabello P S, Ballester R C, et al. Impact of a multidisciplinary team for the management of thrombotic microangiopathy. *PLoS One*. 2018;13(11):e0206558. Published 2018 Nov 2. doi:10.1371/journal.pone.0206558
33 Gordon CE, Chitalia VC, Sloan JM, et al, Thrombotic Microangiopathy: A Multidisciplinary Team Approach. Am J Kidney Dis. 2017 Nov;70(5):715-721. doi:
34 Gallan AJ, Chang A. A New Paradigm for Renal Thrombotic Microangiopathy. Semin Diagn Pathol. 2020 May;37(3):121-126. doi: 10.1053/j.semdp.2020.01.002. Epub 2020 Feb 6. PMID: 32085935.
35 Zini G, De Cristofaro R. Diagnostic Testing for Differential Diagnosis in Thrombotic Microangiopathies. *Turk J Haematol*. 2019 Nov 18;36(4):222-229. doi: 10.4274/tjh.galenos.2019.2019.0165. Epub 2019 Jul 24. PMID: 31337190; PMCID: PMC6863018.
36 An international consensus approach to the management of atypical hemolytic uremic syndrome in children - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Diagnostic-algorithm-for-atypical-HUS-in-children-a-Blood-sampling-imperatively-before_fig1_281838127 [accessed 14 Feb 2022]
37 Fakhouri F, Scully M, Management of thrombotic microangiopathy in pregnancy and postpartum: report from an international working group, *Blood Vol 136, Number 19 , 2020*
38 Ávila A, Gavela E, Sancho A. Thrombotic Microangiopathy After Kidney Transplantation: An Underdiagnosed and Potentially Reversible Entity. *Front Med (Lausanne)*. 2021;8:642864. Published 2021 Apr 8. doi:10.3389/fmed.2021.642864
39 Berger BE. Atypical hemolytic uremic syndrome: a syndrome in need of clarity. Clin Kidney J. 2018 Jul 31;12(3):338-347. doi: 10.1093/ckj/sfy066. PMID: 31198222; PMCID: PMC6543964.
40 Bhise V, Meyer A N D, Menon S et al, Patient perspectives on how physicians communicate diagnostic uncertainty: An experimental vignette study, *International Journal for Quality in Health Care*, Volume 30, Issue 1, February 2018, Pages 2–8, https://doi.org/10.1093/intqhc/mzx170
41 Blasco, M, Guillén, E, Quintana L F, et al, Thrombotic microangiopathies assessment: mind the complement, *Clinical Kidney Journal*, Volume 14, Issue 4, April 2021, Pages 1055–1066, https://doi.org/10.1093/ckj/sfaa195
42 Gianluigi Ardissino, Selena Longhi, Luigi Porcaro, et al, Risk of Atypical HUS Among Family Members of Patients Carrying Complement Regulatory Gene Abnormality, *Kidney International Reports*,Volume 6, Issue 6,2021,Pages 1614-1621,ISSN 2468-0249,https://doi.org/10.1016/j.ekir.2021.03.885. (https://www.sciencedirect.com/science/article/pii/S2468024921010330)
43 Noris M, Caprioli J, Bresin E, et al, Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol. 2010 Oct;5(10):1844-59. doi: 10.2215/CJN.02210310. Epub 2010 Jul 1. PMID: 20595690; PMCID: PMC2974386.ver%20uremic.%E2%80%9D
44 Kurian, C.J., French, Z., Kukulich, P. *et al.* Case series: coronavirus disease 2019 infection as a precipitant of atypical hemolytic uremic syndrome: two case reports. *J Med Case Reports* **15,** 587 (2021). https://doi.org/10.1186/s13256-021-03144-2
45 The national aHUS Service Annual Report016/17 page 18, Fig 6. National Renal Complement Therapeutics Centre https://www.atypicalhus.co.uk/wp-content/uploads/2018/03/NRCTC-Annual-Report.pdf Retrieved 12 November 2021.
46 Kidney Research UK, News 6 May 2020, https://kidneyresearchuk.org/2020/05/06/kidney-research-uk-wins-national-film-award/, Retrieved 12 November 2021.
47 Palma LMP, Sridharan M, Sethi S. Complement in Secondary Thrombotic Microangiopathy. *Kidney Int Rep*. 2021;6(1):11-23. doi:10.1016/j.ekir.2020.10.009
48 Avila Bernabeu A, I, Cavero Escribano T, Cao Vilarino M: Atypical Hemolytic Uremic Syndrome: New Challenges in the Complement Blockage Era. *Nephron* 2020;144:537-549. doi: 10.1159/000508920
49 Mayo Clinic Laboratory, Test ID :aHUSP, Complement-mediated Atypical Hemolytic-Uremic Syndrome (aHUS)/Thrombotic Microangiopathy (TMA) Genetic Panel , Values , 2022 https://www.mayocliniclabs.com/test-catalog/Overview/64663 Retrieved 7 February 2022
50 atypical Hemolytic Uremic Syndrome Genetic Susceptibility Panel , Cincinnati Children's Hospital www.cincinnatichildrens.org/-/media/cincinnati%20childrens/home/service/d/diagnostic-labs/.../atypical-hemolytic-uremic-syndrome-ahus-panel.pdf Retrieved 7 February 2022

51 Machaon Clinic Laboratories Test, AHUS GENETIC PANEL, https://www.machaondiagnostics.com/panel/ahus-genetic-panel/ Retrieved 7 February 2022.
52 Bresin E, Rurali E, Caprioli J, et al , European Working Party on Complement Genetics in Renal Diseases. Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol. 2013 Feb;24(3):475-86. doi: 10.1681/ASN.2012090884. Epub 2013 Feb 21. PMID: 23431077; PMCID: PMC3582207.
53 Bu F, Meyer NC, Zhang Y, Borsa NG, Thomas C, Nester C, Smith RJ. Soluble c5b-9 as a biomarker for complement activation in atypical hemolytic uremic syndrome. *Am J Kidney Dis*. 2015 Jun;65(6):968-9. doi: 10.1053/j.ajkd.2015.02.326. Epub 2015 Mar 25. PMID: 25818678.
54 Timmermans, S A, Abdul -Hamid, M, Potjewijd J et al, on behalf of the Limburg Renal Registry C5b9 Formation on Endothelial Cells Reflects Complement Defects among Patients with Renal Thrombotic Microangiopathy and Severe Hypertension JASN August 2018, 29 (8) 2234-2243 ; DOI: https://doi.org/10.1681/ASN.2018020184
55 Palma L M P, Sanjeev S, Thrombotic microangiopathy and their mimickers, *Nephrology Dialysis Transplantation*, 2020;, gfaa230, https://doi.org/10.1093/ndt/gfaa230
56 Complement Prospective Evaluation of Thrombotic Microangiopathy on Endolethium, ClinicalTrials.gov identifier: NCT 0474519. Updated 23 August 23, 2021. Accessed February 7, 2022, https://clinicaltrials.gov/ct2/show/record/NCT04745195?cond=aHUS&draw=2&rank=37&view=record
57 Ravulizumab in Thrombotic Microangiopathy Associated With a Trigger, ClinicalTrials.gov identifier: NCT04743804. Updated December 3, 2021. Accessed 7 February 2022 https://clinicaltrials.gov/ct2/show/NCT04743804?term=aLEXION&recrs=a&draw=2&rank=6
58 Burwick, R M, Feinberg, B B, Complement activation and regulation in preeclampsia and hemolysis, elevated liver enzymes, and low platelet count syndrome ,*American Journal of Obstetrics and Gynecology*, Volume 226, Issue 2, Supplement,2022, Pages S1059-S1070,ISSN 0002-9378, https://doi.org/10.1016/j.ajog.2020.09.038.
59 Bayer G, von Tokarski F, Thoreau B, et al , Etiology and Outcomes of Thrombotic Microangiopathies. *Clin J Am Soc Nephrol*. 2019 Apr 5;14(4):557-566. doi: 10.2215/CJN.11470918. Epub 2019 Mar 12. PMID: 30862697; PMCID: PMC6450353.
60 Gupta M, Govindappagari S, Burwick RM. Pregnancy-Associated Atypical Hemolytic Uremic Syndrome: A Systematic Review. *Obstet Gynecol*. 2020;135(1):46-58. doi:10.1097/AOG.0000000000003554
61 Raina, R., Sethi, S.K., Dragon-Durey, MA. *et al.* Systematic review of atypical hemolytic uremic syndrome biomarkers. *Pediatr Nephrol* (2022). https://doi.org/10.1007/s00467-022-05451-2
62 Hideo Wada, Katsuya Shiraki, Takeshi Matsumoto, *et al* , The evaluation of a scoring system for diagnosing atypical hemolytic uremic syndrome, *Thrombosis Update, Volume 1,*2020,100012,ISSN 2666-5727 ,https://doi.org/10.1016/j.tru.2020.100012
63 Palma, L.M.P., Vaisbich-Guimarães, M.H., Sridharan, M. *et al.* Thrombotic microangiopathy in children. *Pediatr Nephrol* (2022). https://doi.org/10.1007/s00467-021-05370-8
64 aHUS alliance Global Action, aHUS nomenclature group project , *www.ahusallianceaction,org* https://www.ahusallianceaction.org/13375-2/
65 Washington University School of Medicine in St Louis ,John T Milliken Department of Medicine, Division of Nephrology https://nephrology.wustl.edu/dr-anuja-java-co-chairs-working-group-for-revising-ahus-nomenclature/#:~:text=The%20term%20'aHUS'%20was%20coined,hemolysis%20and%20almost%20ne