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aHUS Diagnosis Process: Impact of process event and patient demographic variables on process outcomes.

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ABSTRACT

Background

Rare diseases present a diagnosis challenge for clinicians. The rare disease atypical Hemolytic Uremic Syndrome (aHUS) manifests as a medical emergency due to a condition known as thrombotic microangiopathy (TMA). To diagnose and treat aHUS a clinician must first recognise the TMA, and next decide on its cause, then treat it. An incorrect, or untimely, diagnosis can result in poorer health outcomes. Globally, patients believe the process for diagnosing aHUS is not satisfactory and can be improved.

Method

We collected data from 227 aHUS patients using a 42-question online survey instrument. Here we use the data to identify factors which significantly influence outcomes of health, treatment burden and perception of the diagnosis process.

Results

We found diagnosis outcomes were influenced by some health care system event or patient demographic variables. Patient age and the era of diagnosis showed significant differences on one, or two, of the process outcomes. However, timelines needed by clinicians to make a correct aHUS diagnosis were a significant factor across all outcomes**.** Rapid accurate diagnoses led to significantly better health state, lower treatment burden, and a more positive process perception**.** Misdiagnosis was the key contributor to delay in an aHUS diagnosis and in the poorer outcomes.

Conclusion

Patients with aHUS face difficulties in receiving a timely accurate diagnosis. Most patients are initially misdiagnosed, particularly with Thrombotic Thrombocytopenic Purpura (TTP) and experience a prolonged delay before the error is corrected, sometimes lasting years. Diagnosis timelines have had a significant effect on health and treatment burden outcomes. Improvements to the process through education and awareness are still needed.

Key learning points

- **Diagnosis of aHUS is significantly prolonged by misdiagnosis**
- **Almost two thirds of aHUS patients are misdiagnosed**
- **13% of patients, mainly female adults, remain misdiagnosed for more than a year**
- **A TTP diagnosis is the most common diagnosis error**
- **Misdiagnosis impacts adversely on health, treatment burden and patient anxiety/confidence perception outcomes**

Introduction

Rare diseases are difficult to diagnose[1] and atypical Hemolytic Uremic Syndrome (aHUS) is a rare disease by any definition of the term rare disease.[2,3,4,5,6] It is caused by dysregulation of an intrinsic part of the innate immune system called Complement.[7] aHUS mostly presents as a medical emergency due to the manifestation of a thrombotic microangiopathy, or TMA. aHUS is a rare cause of a TMA, and its diagnosis is arrived at by first excluding other TMA causes.[8] A TMA is characterised by low platelet levels, microangiopathic hemolytic anaemia and damage to at least one organ.[9] Most causes of TMA are identified within 7 days or less of presentation.[10] However less than half of aHUS patients are diagnosed in that time and many aHUS patients are misdiagnosed.[11] Diagnostic error of aHUS, whether incorrect or untimely, can potentially result in worse health and treatment outcomes.[12] Clinicians and patients believe that the aHUS diagnosis process can be improved.[13]

The complexities of health outcome improvement are challenging.[14] Models exist for disease specific patient expectations of health care, and patients generally describe their expectations in terms of health outcomes, individual clinicians and the health care systems.[15] As far as is known no specific model exists for aHUS.

In their research agenda aHUS patients identified that there could be a point in the diagnosis process where delay by clinicians in making a diagnosis and administering effective treatment would have catastrophic consequences to the health outcomes.[16] By inference they also recognise that non-catastrophic process outcomes are also attainable resulting in better health and also lower treatment burden. 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) after an aHUS presentation, than for those treated late.[17]

Patient organisations are increasingly undertaking research to understand the diagnosis process for their disease.[18] aHUS alliance Global Action, an incorporated patient advocacy charity, has undertaken a survey of global aHUS patients' experience of the aHUS diagnosis process and results have been reported.[11,19.20]

In this report of aHUS patients' real-world experiences, a drill down has been conducted into process events and patient demographic variables to determine what factors have positively, or negatively, influenced process outcomes and how significant they have been.

Method

An online questionnaire, using a six section SurveyMonkey instrument comprised of 42 questions, 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.[21] 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.

The questionnaire was structured around the steps in a clinical diagnosis process model conceptualised by the USA Institute of Medicine Committee on Diagnostic Error in Health Care.[22] 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 and outcomes. 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 unwieldy. Our concise questionnaire design, therefore, presents the broader experience to provide more insight with succinct clarity.

Using the data acquired, indices have been constructed for outcomes of current health state, current treatment burden and process perception. Each index was derived from weighting the range of reported results from the best to worst outcomes. For the current health state index (HSI) the EQ-5D levels from Excellent-score of 5, down to Very Poor- score of 1, were used.[23] Treatment burden is the effort required from patients to look after their health and the impact this has on their functioning and wellbeing.[24] A simple index was constructed for the study to measure current treatment burden utilising the following rating scale: no treatment remission- score of 5, complement inhibitor only- score of 4, kidney transplant without complement inhibitor- score of 3, kidney transplant with complement inhibitor- score of 2 and dialysis- score of 1. The perception index (PI) was based on most favourable opinion, with score of 4, to most unfavourable opinion scoring 1, as related to the difficulty of a diagnosis and any resulting anxiety/loss of confidence. The aggregate scores for each variable were divided by the number of patients reporting to produce an average index.

Indices were calculated for each of the key clinical process events and patient demographics for each outcome. Clinical process event and demographic ariables included are shown in Fig 1 below. For each outcome, variables are shown in descending order from best to worst outcome. A simple chi square test at *p value p = .05* was also undertaken for each variable to gauge its level of significance. An overall index has been included in each table to delineate the variables which influenced outcomes more positively or negatively.

Fig. 1 Process events and patient demographic variables

Process Events	Patient demographics
Care status at time of aHUS onset	Gender
Delay in escalation to specialist care	Age
Clinical condition on arrival in specialist care	Continental region
Specialism of treating clinician	Era of diagnosis
Having a kidney failure symptom	Family history of aHUS
Health state at time of diagnosis	Confirmed genetic susceptibility
Current health state	
Current treatment	
Timelines	

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.[25] 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.[26] 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.

Results

The three high-level outcomes of the aHUS diagnosis process are, the patients' current health state, the ongoing treatment burden and the patients' perception of the process.

Current Health State

Table 1 shows the reported current self-declared health state at the time of participation in the study and prior to illness using a version of the EQ-5D instrument. Eighty seven percent of patients reported their current health being "Good to Excellent". The overall health state index (HSI) reveals a current health outcome of 3.43/5 which was less than the overall HSI of 3.81/5 that patients reported prior to illness. Infants report a fall in HSI from 3.94/5 prior to illness to 3.61/5 and older children report a slight improvement from 3.69/5 to 3.81/5. The outcome HSI of 3.23/5 reported by adults was much less than was reported pre-illness, i.e., a HSI of 3.82/5.Two adult male patients had died following diagnosis.

Table 1 Patients self-declared health state at time of participation in study and prior to illness

At time of study participation		
Health state:	**No**	**%**
Excellent	25	11.01
Very Good	77	33.92
Good	96	42.29
Poor	23	10.13
Very Poor	4	1.76
Deceased	2	0
Total	227	100
	HSI	
All	3.43	
Infants (36)	3. 61	
Older children (42)	3.81	
Adults (149)	3.23	

Prior to illness		
Health state:	**No**	**%**
Excellent	72	31.71
Very Good	78	34.36
Good	51	22.46
Poor	30	13.21
Very Poor	11	4.84
Deceased	0	0
Total	227	100
	HSI	
All	3.81	
Infants (36)	3.94	
Older children (42)	3.69	
Adults (149)	3.82	

Current health state- influencing variables

Clinical Process Event Variables

In Table 1.1, the HSIs of key clinical process event variables are presented in descending order from highest health state to lowest around the overall average.

A rapid diagnosis **timeline***, i.e., 7 days or less, or moderate timeline i.e., 8 to 31 days diagnosis had the highest positive influence on current health with HSIs of 3.66/5 and 3.57/5 respectively. Conversely a prolonged diagnosis timeline resulted in a significantly low HSI at 2.92/5 *(p value .0001 , p <.05*).

Patients with an ongoing treatment status as on dialysis reported the significantly lowest HSI, 2.62/5 (*p value .0001, p <.05*). A significantly low HSI result, 3.0/5 (*p value ,0008, p< .05)*. was also reported by the few patients currently treated with a kidney transplant without a complement inhibitor.

HSIs relating to clinical **condition*** on arrival in specialist care, the profession of the treating **specialist***, and **care status*** at time of aHUS onset varied but with no significant differences.

Table 1.1 Impact of key process events on current health state outcome

		Excellent	Very Good	Good	Poor	Very Poor		
Event Category	**Specific variables**	**No.**	**No.**	**No.**	**No.**	**No.**	**HSI**	***p-value p = .05***
Timeline	**1-7 days**	19	39	43	6	0	3.66	.0692
Timeline	**8-31 days**	4	27	17	5	0	3.57	.1207
Condition	**Critical**	7	29	29	4	0	3.57	.4278
Specialist	**Haematologist**	2	15	16	1	0	3.53	.3630
Treatment	**None**	5	18	23	3	0	3.51	.7333
Specialist	**Nephrologist**	13	28	40	8	1	3.49	.8083
Condition	**Other**	13	29	32	10	2	3.48	.7064
Treatment	**CI**	18	42	52	11	3	3.48	.7795
Care status	**Not in care**	25	68	89	20	4	3.44	.9839
Specialist	**Oncol/Ped**	0	3	4	0	0	3.43	.7148
Overall	**Overall**	**25**	**77**	**96**	**23**	**4**	**3.43**	**1.000**
Treatment	**Ktx+**	2	12	16	1	1	3.41	.5432
Care status	**In care**	0	9	7	3	0	3.32	.3879
Condition	**Life threatening**	5	19	35	9	2	3.23	.4289
Specialist	**MDT**	9	30	32	14	4	3.29	.1179
Treatment	**Ktx -**	0	2	1	0	1	3.00	.0088
Timeline	**Over 31days**	2	11	36	12	4	2.92	.0001
Treatment	**Dialysis**	0	2	4	7	0	2.62	.0001

*Categories: Timeline – time to diagnosis in specialist care, Condition – clinical condition on arrival in specialist care, Specialist- specialism of treating clinician, Care status- care at time of aHUS onset, Treatment – current treatment burden.

Patient Demographic Variables

Of the patient demographic variables that are reported in Table 1.2, only **age** showed markedly different influences. Under 18-year-old patients reported a significantly high HSI at 3.72/5 (*p value .0184, p < .05)* and older adults (45 years or more) report the worst health state 3.11/5, although not significantly *(p value .0567, p >..05*).

Gender, region, **era** of diagnosis, or having a genetic **variant** susceptibility were not significantly different. Even knowledge of a family **history** of aHUS made no significant difference. Patients without a family history of aHUS reported a higher HSI than those who knew. The latter may be the result of several long-term misdiagnosed patients becoming aware of other family members to trigger a reappraisal of a misdiagnosis.

Table 1.2 Impact of patient demographics on current heath state outcomes

		Excellent	Very Good	Good	Poor	Very Poor		
Demographic Category	**Specific Variable**	**No.**	**No.**	**No.**	**No.**	**No.**	**HSI**	***p-value p = .05***
Age	**Older children**	10	16	14	2	0	3.81	.0584
Age	**All <18 years**	16	31	26	3	2	3.72	.0184
Age	**Infants**	6	15	12	1	2	3.61	.1276
Gender	**Male**	7	25	24	9	2	3.51	.0541
Region	**Europe**	6	22	23	7	0	3.47	.8066
Era	**Pre 2011**	5	11	16	4	0	3.47	.8965
Variant	**Yes**	20	60	66	18	2	3.47	.9084
Gender	**Female**	18	52	70	14	2	3.45	.9522
Era	**2011-2015**	6	23	24	6	1	3.45	.9764
History	**None**	22	72	89	18	3	3.45	.9595
Overall	**Overall**	**25**	**77**	**96**	**23**	**4**	**3.43**	**1.000**

Table 1.2 Continued

Demographic Category	Specific Variable	No.	No.	No.	No.	No.	HSI	*p-value p = .05*
Region	**North Americas**	19	43	61	14	4	3.42	.7000
Era	**Post 2015**	14	43	56	13	3	3.40	.9914
Region	**Rest of World#**	0	12	12	2	0	3.38	.3229
Variant	**No**	5	17	29	5	2	3.31	.6411
Age	**Young adults**	7	37	48	13	4	3.28	.3182
Age	**All 18 year or >**	9	44	70	20	4	3.23	.1203
History	**Not known**	1	2	4	2	0	3.22	.7700
History	**Known**	2	3	3	3	1	3.17	.1372
Age	**Older adults**	2	7	22	7	0	3.11	.0567

*Categories : Age- at time of diagnosis, Gender- Male female or other, Region- Continent, Era- when diagnosis made, Variant- confirmed predisposing Complement mutation, History- Family history of aHUS # Africa-2, Asia-10, Oceania-12, South Ameica-2.

Current Treatment Burden

Table 2 shows the current treatments reported by patients at the time of participation in the study. The treatments are limited to those needed to control complement activity and/or for renal replacement therapy for those who have suffered renal failure as a consequence of aHUS. Other treatments for comorbidities, such as high blood pressure or immunosuppressants for transplants were not asked for in the study questionnaire.

The majority of patients (70%) reported being treated with a complement inhibitor, i.e., eculizumab or another complement inhibitor drug in trial. For four in five of those patients a complement inhibitor was their only treatment; for the remainder the complement inhibitor was being used to support a kidney transplant. Most transplant patients were adults. Four transplant patients were not receiving a complement inhibitor, one of the four had a combined liver kidney transplant. Six per cent of patients were on dialysis and two patients had died following diagnosis.

The overall treatment burden index (TBI) reported by patients was 3.74/5. Patients under 18 years old were found to have a lower treatment burden, with a TBI at 4.06/5, than adult patients, TBI 3.57/5.

Table 2 – Treatment burden current at time of participation in study

Treatment	All	%	Under 18 years	%	Over 18 years	%
No treatment - in remission	49	22	23	30	26	17
Complement inhibitor	126	56	46	59	80	54
Transplant without complement inhibitor	4	1	1	1	3	2
Transplant with complement inhibitor	32	14	7	9	25	17
On Dialysis	13	6	1	1	12	8
Deceased	2	1	-	-	2	1
No reply	1	-	-	-	1	1
Total	227	100	78	100	149	100
Treatment Burden	3.74		4.06		3.57	

Current treatment burden- influencing variables

Clinical Process Event Variables

In table 2.1, events in the diagnosis process are presented in descending order of TBI from least burdensome treatment to the most burdensome.

Patients receiving the most rapid diagnosis in 7 days or less reported a significantly lower treatment burden TBI, 4.01/5 (*p value* .0469 *, p < .05)* . Whereas those with a prolonged diagnosis timeline reported a significantly higher treatment burden, a TBI of 3.36/5 (*p value .0004, p < .05*)

Current health made a difference to TBI outcomes. Those in very poor and poor health reporting high treatment burdens with TBIs of 3.55/5 and 3.14/5 respectively, the latter being significantly higher (*p value .0128, p < .05), w*hereas those in excellent health reported the lowest treatment burden, TBI 4.04/5

The other variables clinical condition on arrival in specialist care, health state at **diagnosis**, treating specialist, or being in care at onset for another condition varied but not significantly.

Table 2.1 Process events impact on current treatment burden.

		Remission	CI*	KTx** -CI	KTx +CI	Dialysis		
Event Category	**Specific variable**	**No.**	**No.**	**No,**	**No.**	**No.**	**TBI*** **	***p-value p = .05***
Diagnosis	**Very Good**	2	1	0	0	0	4.66	-
Health	**Excellent**	5	18	0	2	0	4.04	.4435
Timeline	**1-7 days**	24	72	2	6	3	4.01	.0469
Specialist	**Oncologist/Ped.*** **	1	6	0	1	0	3.88	.8360
Specialist	**MDT**** **	22	51	1	8	6	3.85	.6509
Condition	**Critical**	14	43	3	8	2	3.84	.3615
Health	**Very Good**	18	42	3	12	2	3.81	.4787
Specialist	**Haematologist**	8	19	0	6	1	3.79	.8443
Health	**Good**	22	53	1	16	4	3.76	.8801
Diagnosis	**Poor**	11	31	1	7	3	3.75	.9981
Condition	**other**	22	44	0	10	8	3.74	.3111
Care status	**In care**	4	10	1	4	0	3.74	.5497
Care status	**Not in care**	45	116	3	28	13	3.74	.9005
Overall	**Overall**	**49**	**126**	**4**	**32**	**13**	**3.74**	**1.0000**
Diagnosis	**Very Poor**	32	89	3	24	8	3.72	.9807
Diagnosis	**Good**	4	5	0	1	2	3.67	.3892
Timeline	**8-31 days**	9	31	1	5	5	3.67	.6030
Condition	**Life threatening**	13	39	1	14	3	3.64	.6842
Specialist	**Nephrologist**	17	48	3	17	6	3.58	.5387
Health	**Very Poor**	0	3	0	1	0	3.55	.7814
Timeline	**Over 31 days**	16	23	1	21	5	3.36	.0004
Health	**Poor**	4	10	0	1	7	3.14	.0001
Diagnosis	**Excellent**	0	0	0	0	0	0	-

*CI -Complement Inhibitor, **KTx- Kidney Transplant , ***Ped-Pediatrician, ****MDT – Multi Disciplinary Team

Patient Demographic Variables

Table 2.2 shows patient characteristics that could impact on treatment burden outcome. Gender, genetic variant susceptibility, family history and continental region made no significant difference.

There was a significant difference in treatment burdens between era when diagnosis was made. Patients diagnosed prior 2011 report the highest treatment burden TBI, 3.11/5 *(p value .0012 , p < .05)* whereas those diagnosed post 2015 report a significantly low treatment burden 4.01/5 (*p value .0381, p < .05*). Although not significant, patients diagnosed in the period 2011 to 2015 also reported a higher treatment burden due the higher proportion of patients with a kidney transplant following eculizumab becoming more accessible and a transplant catch up for dialysis patients held back because transplants were not advocated without eculizumab support.

Patients under 18 years old reported the lowest treatment burden with TBIs of 4.12/5 and 4.03/5 for infants and older children respectively.

Table 2.2 Impact of patient characteristics on treatment burden outcome

		Remission	CI*	KTx** -CI	KTx +CI	Dialysis		
Demographic Category	**Specific Variable**	**No.**	**No.**	**No.**	**No.**	**No.**	**TBI**	***p-value p = .05***
Age	**Older children**	12	26	1	3	0	4.12	.2715
Age	**Infants**	11	20	1	3	1	4. 03	.5743
Era	**Post 2015**	34	80	1	7	6	4.01	.0381
Variant	**No**	11	40	0	4	3	3.90	.2689
Region	**Europe**	21	23	1	10	3	3.84	.0695
Gender	**Female**	34	91	3	19	8	3.80	.9459
Region	**Rest of World**	7	13	2	1	3	3.77	.0606
Overall	**Overall**	**49**	**126**	**4**	**32**	**13**	**3.74**	**1.0000**
Region	**North Americas**	21	90	1	21	7	3.69	.2195
Variant	**Yes**	38	85	4	28	10	3.68	.7383
Gender	**Male**	14	35	1	12	5	3.61	.8801
Age	**Older adults**	4	25	0	5	3	3.59	.4158
History	**Known**	3	5	1	2	1	3.58	.4675
History	**Not known**	2	5	0	0	2	3.56	.2286
Age	**Young adults**	22	55	2	21	9	3.55	.4313
Era	**2011-2015**	8	35	1	14	2	3.55	.1902
Gender	**Other**	1	0	0	1	0	3.50	.4357
Era	**Pre 2011**	7	11	2	11	5	3.11	.0012

Perception of diagnosis process

Perception was measured using four "descriptive vignettes" from a most favourable perception to a most unfavourable, based on the ease or difficulty of receiving an aHUS diagnosis and any resultant impact of anxiety and loss of confidence from the experience.

Table 3 presents the perceptions reported by patients. The majority of patients (57%) reported an overall more favourable perception of the process; 37% of patients perceived it as favourable and 20% most favourable. A minority of patients (43%) were left either recalling a feeling of anxiety because of their clinician's uncertainty (24%) or had low confidence (19%) in the process due to the time it took to get a diagnosis. The overall Perception Index (PI) was 2.58/4.

Table 3 Perception of the diagnosis process

Perception	Vignette	No.	%
Most favourable	**It was not approached any differently from other healthcare issues, so I felt relaxed about getting info & options**	44	20
Favourable	**It was a little more complicated than I thought it would be to get an explanation, but felt confident about it**	84	37
Unfavourable	**I was extremely anxious that doctors did not seem to know what I had and what to do**	55	24
Most unfavourable	**I did not know how hard and prolonged it would be to get a diagnosis of what was wrong with me, my confidence was really shaken**	42	19
	Total	225	100
	No opinion	2	-

Perception Index (PI)	2.58

Perception of process- influencing variables

Process event variables

In Table 3.1 the impact of process event variables is presented. Time spent in specialist care up to a diagnosis being made has a significantly different impact on patients' perception of the diagnosis process. Those diagnosed rapidly in 7 days or less had the highest favourable opinion PI 3.0/4 (*p value .0001, p < .05*) and those experiencing a prolonged diagnosis time over 31 days found it unfavourable PI 2.03/4 (*p value .0001, p < .05*). Patients with transplants supported by a complement inhibitor also reported a significantly unfavourable process perception with a PI of 2.13/4 (*p value .0334 p < .05*)

Other process events variables, current health state, care specialists and care status at onset made no significant difference to patients' perception of the process.

An additional variable was examined for perception. Patients had also been asked about how "holistic" their care had been from a clinical approach which was concerned only with **physical care** or **anxieties** to that which addressed the wider **challenges** or **burdens** patients faced. Patients who felt their wider challenges or burdens were addressed reported a more favourable perception of the process, but not significantly.

Table 3.1 Process events variable - on patient perception

		Most Favourable	Favourable	Unfavourable	Most Unfavourable		
Event Category	**Specific variable**	**No.**	**No.**	**No.**	**No.**	**PI**	***p-value p = .05***
Timeline	**1-7**	33	51	13	10	3.00	.0001
Treatment	**KTx - CI**	1	2	1	0	3.00	.8061
Health	**Excellent**	7	10	7	1	2.92	.2647
Health	**Very Good**	18	34	13	12	2.75	.2923
Approach	**Burdens**	15	21	9	10	2.75	.3673
Specialist	**Nephrologist**	25	30	22	14	2.73	.2714
Specialist	**Oncol/Ped**	2	2	2	1	2.71	.9065
Health	**Poor**	4	11	5	3	2.70	.7549
Approach	**Challenges**	16	23	11	12	2.69	.4945
Treatment	**None**	10	21	8	9	2.67	.6242
Treatment	**CI**	26	50	30	19	2.66	.7645
Care Status	**In care**	5	3	9	2	2.58	.0559
Care Status	**Not in care**	39	81	46	40	2.58	.8737
Overall	**Overall**	**44**	**84**	**55**	**42**	**2.58**	**1.000**
Specialist	**MDT**	11	37	23	16	2.49	.4074
Approach	**Physical care**	10	32	29	12	2.48	.0734
Treatment	**Dialysis**	4	2	3	4	2.46	.3151
Timeline	**8-31**	6	17	19	9	2.39	.1541
Health	**Good**	15	27	29	23	2.36	.1237
Specialist	**Haematologist**	5	11	8	9	2.36	.6195
Approach	**Anxieties**	2	4	4	4	2.29	.7243
Treatment	**KTx +CI**	3	7	13	9	2.13	.0334
Timeline	**Over 31**	5	15	24	23	2.03	.0001
Health	**Very Poor**	0	1	2	1	2.00	.5519

Patient demographic variables

Table 3.2 shows the effect patient demographics had on perception. Patients under 18 years had a significantly more favourable perception of the process 2.84/4 *(p value .0196, p < .05*) than adults 2.44/4. There were no significant perception differences arising from gender or continental region variables but those diagnosed before 2011 had the most significantly unfavourable perception of the process with a PI of 2.36/4 (*p value .0404, p < .05*). The two other gender patients reported the most unfavourable perception of the process.

Table 3.2 Impact of patient characteristics on perception of the diagnosis process

		Most favourable	Favourable	Unfavourable	Most Unfavourable		
Demographic Category	Specific Variable	No.	No	No	No	PI	*p-value p = .05*
Age	**infant**	9	19	5	3	2.94	.0879
Age	**<18**	16	40	12	8	2.84	.0196
Age	**Older child**	7	21	7	5	2.75	.2452
Gender	**Male**	13	30	19	7	2.71	.2993
Region	**Europe**	12	22	15	8	2.67	.8431
Era	**Post 2015**	27	49	29	23	2.63	.9430
Era	**2011-15**	11	23	19	8	2.61	.5313
Region	**Rest of World**	5	10	5	5	2.60	.9644
Overall	**Overall**	**44**	**84**	**55**	**42**	**2.58**	**1.000**
Region	**North Americas**	27	52	35	29	2.54	.9658
Gender	**Female**	31	54	35	34	2.53	.7092
Age	**Older adults**	7	13	11	8	2.49	.9154
Age	**All > 18 years**	28	44	43	34	2.44	.1689
Age	**Young adults**	21	31	32	26	2.43	.1787
Era	**Pre 2011**	6	12	7	11	2.36	.0404
Gender	**Other**	0	0	0	2	1.00	.0333

Timelines to diagnosis

Table 4 shows the timelines for referral to specialists after first seeking medical advice and time spent in specialist care until an accurate diagnosis of aHUS is made. Although no diagnosis certainty emerges in Primary Care, most patients are rapidly referred to specialist care, 75% in less than 7 days. It is in specialist care that an aHUS diagnosis is eventually made, but only 48% of patients get a rapid diagnosis i.e., in 7 days or less of presentation. Sixty-nine (30%) of patients experience a prolonged diagnosis odyssey, thirty (13%) remaining misdiagnosed for more than a year.

Table 4 Timeline for referral to specialists and in specialist care up to a diagnosis

	Referral	To Specialist	To Specialist	Diagnosis
Timeline	No.	%	No	%
Up to Day 7	170	75	107	48
8 to 31 days	32	14	51	22
Over 31 days *	25	11	69	30
Total	227	100	227	100
*** inc. Over 365 Days**	7	3	30	13

Table 4.1 lists the process events influencing diagnosis timeline in specialist care in descending order of Timeline Speed Index (TSI) (based on “Up to Day 7” -scores 3 , “8-31days”- scores 2 and “Over 31 days”- scores 1) .

Kidney failure is a hallmark feature of aHUS and so this **symptom** was included as a specific variable. However, patients reporting a kidney failure/injury symptoms experienced a similar diagnosis timeline as those who reported no such symptoms. TSIs of the treating clinician specialisms did vary, but not significantly.

Timelines were most influenced by whether or not a patient was diagnosed with another cause of TMA before an aHUS diagnosis. Patients reporting that aHUS was their only diagnosis had a significantly higher TSI, 2.79/3 (*p value .0001, p < .05*). The TSI for those who recalled no other cause was also higher, 2.49/3 (*p value .0511, p < .05*) but not significantly, whereas those reporting a Pregnancy TMA, Other TMA or TTP as alternative or

misdiagnoses, experienced the longest timelines. aHUS patients with a TTP misdiagnosis in particular experienced significantly longer timelines and thus a lower TSI, 1.69/3 (*p value .0001, p <.05*).

One other observation concerned those patients whose **referral** from Primary Care was delayed. They also reported a significantly lower TSI and delay to diagnosis in specialist care *(p value .0156, p < .05*)

Table 4.1 Process events Impact on clinical diagnosis timeline

Event Category	Specific variable	1- 7	8-31	32+	TSI	*p-value p = .05*
Diagnosis	**No cause other than aHUS**	28	3	2	2.79	.0001
Diagnosis	**TTP/HUS**	10	3	2	2.53	.2707
Diagnosis	**No other cause recalled**	27	10	6	2.49	.0511
Specialist	**Oncology/Paediatrician**	4	3	1	2.38	.4226
Specialist	**MDT**	46	24	20	2.29	.2128
Diagnosis	**Uncertain renal failure**	4	1	2	2.29	.8467
Referral	**Prompt**	89	38	42	2.28	.2666
Specialist	**Haematologist**	18	6	10	2.24	.7739
Symptom	**No kidney failure/injury**	20	7	13	2.18	.7867
Symptom	**Kidney failure/injury**	87	44	56	2.17	.8835
Overall	**Overall**	**108**	**50**	**69**	**2.17**	**1.000**
Specialist	**Nephrologist**	37	18	37	2.00	.1213
Diagnosis	**Other condition**	3	1	4	1.88	.4696
Diagnosis	**HUS**	8	7	12	1.85	.1520
Referral	**Delayed**	18	13	27	1.84	.0156
Diagnosis	**P-TMA**	4	2	8	1.71	.0936
Diagnosis	**TTP**	14	10	31	1.69	.0001
Diagnosis	**Other TMAs**	1	2	3	1.67	.3148

Discussion

Unless affected by a previous experience of healthcare or, more specifically, an aHUS patient who had observed another family member with aHUS, many patients would enter their care pathway with a dispositional optimism.[27] Patients understandably have expectations that upon visiting their health advisor and obtaining some test results it would follow that they would know quickly what was wrong with them. This would be followed swiftly by appropriate treatment for a short duration, which would be expected to cure their health problem and they would return to their health state before illness. They would not expect to find they had a life threatening, ultra-rare disease which can result in chronic kidney failure necessitating lifelong renal dialysis, or even a kidney transplant operation. In our study of the overall real-world experience of patients, their recovery to health and ongoing treatment burden and experience of the health care process would contrast markedly with those expectations.

The diagnosis process ends with the treatment step.[22] A decision being made by the clinician from the treatments available for the diagnosed condition. For complement mediated aHUS effective treatment is needed to stop uncontrolled complement activity, either with plasma therapy or a complement inhibitor.[28] However, because kidney impairment is the hallmark of aHUS[29] the stage of unrecoverable kidney failure reached during the diagnosis process can result in ongoing renal function replacement therapy i.e., kidney dialysis or kidney transplant with or without a complement inhibitor.[30] This can compound the treatment burden of aHUS patients. The study questionnaire sought not only data about these two current treatment burden outcomes i.e., complement inhibition and/or renal replacement therapy, but also whether patients had reached an untreated remission.[31] It did not elicit other treatments for residual comorbidities e.g., for hypertension, or immunosuppressants for transplants.[32,33]

Seventy-eight per cent of patients did not need long term kidney function replacement therapy and 70% of patients were receiving a complement inhibitor. This complement inhibitor was, almost always, eculizumab. Eculizumab is a monoclonal antibody which blocks C5 of the complement system from continuing to activate the C5b to 9 membrane attack complex.[34] Patients who are in a durable remission, no longer needing a

complement inhibitor, report the best of health outcomes. Significantly poorer health states are reported by those on dialysis or with transplants not supported by eculizumab. aHUS transplant patients who were administered eculizumab reported a higher health state than those without. Studies have found that those who received prophylactic eculizumab for a transplant have better kidney function than those who do not.[35]

Key factors observed in Tables 1.1, 1.2, 2.1, 2.2, 3.1, 3.2 which most positively, or negatively, influenced outcomes from the diagnosis process are summarised in the following table.

Table 5.1 Top and bottom three factors which influenced patients outcomes from the diagnosis process

	Positive Factors	Negative Factors
Outcome	**Specific variable**	**Specific variable**
Health	Timeline 1-7 days	Timeline - over 31 days
Health	Age under 18 years	Treatment -dialysis
Health	Age Older children	Age - older adults
Treatment	Timeline 1-7 days	Timeline -over 31 days
Treatment	Excellent Health	Poor Health
Treatment	Era- Post 2015	Era -pre-2011
Perception	Timeline- 1-7 days	Timeline -over 31 days
Perception	Age -under 18 years	Era- pre-2011
Perception	Infants	KTx plus CI

Age is a factor in better health outcomes. Patients under 18 years old, particularly older children, report a higher current health than adults and that reflects in their perception of the process. aHUS patients on dialysis report significantly lower health. As health and treatment burden would be expected to correlate, those reporting excellent current health have a lower treatment burden than those who report poor health. An improvement in treatment burden has been observed in patients who have been diagnosed in the post 2015 era compared with the burden reported by those diagnosed with aHUS before 2011. Pre 2011 patients have the most unfavourable perception of the aHUS diagnosis process. Access to eculizumab has made a significant difference to treatment burden since being approved by the FDA in 2011.[36] Also, having helped patients when most needed, some patients are stopping eculizumab treatment safely and entering an untreated remission.[37]

The timeline to an accurate diagnosis, however, is a consistent factor which influences all three process outcomes.

Table 5.2 The three top positive and negative variables which influenced diagnosis timelines.

	Positive Factors	Negative Factors
Outcome	**Specific variable**	**Specific variable**
Timeline	aHUS diagnosis only*	Delayed Referral*
Timeline	No other diagnosis recalled*	TTP diagnosis*
Timeline	TTP/HUS	Pregnancy TMA

*Significant – *p value=.05*

Two factors were found to have a significant difference regarding the time taken to arrive at a decision of an aHUS diagnosis.

Patients who were not promptly referred to specialist care continued to experience significant delay. Although the initial onset of this disease is mostly 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.[38] A diagnosis of aHUS must follow in a few hours or days to avoid delaying clinically effective treatment[39] but the overall timelines for the gradual onset aHUS would be recorded as prolonged.

A misdiagnosis of the cause of the TMA, particularly with Thrombotic Thrombocytopenic Purpura (TTP), and the time taken to revise the diagnosis, was the main factor behind prolonged diagnosis timelines.

Most aHUS patients (64%) reported that they were initially misdiagnosed. Sixteen percent of patients reported being told that aHUS was the only cause and 20% did not recall being told about any cause other than aHUS. Both of the aHUS diagnosis only groups experienced a significantly shorter diagnosis timeline. As TMA cause determination usually involves a differential diagnosis strategy,[40,41] some patients may have concluded that TTP/HUS were alternative incorrect diagnoses rather just being considered before exclusion. Most TTP/HUS diagnoses reported were revised within 7 days or less which would suggest they were just differentiated. When, however, alternative diagnoses extend beyond 31 days and remain unrevised, sometimes for years, there has clearly been diagnostic error. Those diagnosed with Pregnancy TMA and TTP were more likely to experience long term misdiagnosis.

Pregnancy is a common trigger of aHUS.[42.] Patients reported diagnoses of pre-eclampsia ,eclampsia or HELPP syndrome before an aHUS diagnosis, with few of them being differentiated rapidly to aHUS. For most, revision to an aHUS diagnosis took several years.

If done, tests for TTP include the baseline levels of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, 13) [43], and for HUS, the existence of Shiga toxin and E.coli bacteria in stool and cultures.[44] These tests can be conclusive within 3 working days in most hospital settings with inhouse testing facilities but outsourcing the tests may add 24/48 hours to the lead time.[45] This would be a sufficient turnaround of results to revise any working diagnosis of TTP and/or HUS and permit an "excluded diagnosis" and thus an arrival at a suspicion of an aHUS diagnosis in 7 days or less from presentation.

The presence of Shiga toxin and or E Coli 0154:H4 would confirm a diagnosis of HUS.[44] The level of ADAMTS13 would rule TTP in or out as a TMA cause if results show it to be less than 5% of normal levels.[46] For some clinicians even 5% to less than 10% of normal levels would confirm a TTP diagnosis.[47] More than 10% of normal level would normally rule out a TTP diagnosis.[48] In a survey, two thirds of clinicians reported that they were not medically convinced that TTP should be ruled out at levels far in excess of 10% claiming reports that 10 to 25% of idiopathic TTP patients present with ADAMTS13 levels between 33% and 100%.[10] The presence of severe ADAMTS13 deficiency supports the clinical diagnosis of TTP but ADAMTS13 activity values alone neither establishes nor excludes a diagnosis of TTP.[49]

There has, however, been an appreciation that cases of aHUS have been inappropriately diagnosed as TTP.[50] If so, it is feasible that a misdiagnosed aHUS patient with high baseline ADAMTS13 levels may respond to plasma exchange therapy and even go into untreated remission as has been found in cases of idiopathic aHUS.[51] A lack of consensus on TTP inclusion/exclusion could explain a continued TTP misdiagnosis for some aHUS patients.

Even if Complement protein levels are tested, such tests are not specific enough to confirm an aHUS diagnosis.[52] A confirming diagnosis from genetic testing could take up to another 28 days and in some cases no genetic cause is found.[53,54,55] It is possible that patients reporting moderately long diagnosis timeline of 8-31 days may be reporting a confirmed rather than a suspected aHUS diagnosis. Any diagnosis taking longer than 31 days would be regarded as untimely and/or a misdiagnosis.

Details of a drill down into the facets of 21 very prolonged (over one year) misdiagnosed patients are presented in Table 6. Of the 21 patients (19 adults, 15 female) there were 11 misdiagnosed with TTP, 4 with HUS, 2 with Pregnancy TMAs and 2 with Other TMAs. The average misdiagnosis timeline was 6 years 5 months. These patients have a significantly unfavourable perception of their diagnosis, PI 1.8/4 *(p value .0042, p < .05).* Similarly, their treatment burden was significantly high, TBI 2.24/5 (*p value .0001, p < .05*). Most (75%) prolonged misdiagnosed patients were either still on dialysis, or had a kidney transplant with, or without, a complement inhibitor. Their current health state is low but not significantly, with a HSI of 3.19/5. Their health state at the time of their revised diagnosis was significantly very low, a HSI 1.62/5 *(p value .0001, p < .05*)

Table 6– Details of the prolonged misdiagnosis patients

Patient	Gender	TMA	Timeline (Days)	Era	Treatment	Current Health	Diagnosis Health	Perception
1	M*	TTP	1482	After 2015	CI	Good	Very poor	MF
2	M	TTP	2982	2011-2015	Dialysis	Poor	Very poor	MUF
3	M	TTP	4380	After 2015	KTx+	Very Good	Very poor	UF
4	F	HUS	3050	Pre 2011	KTx+	Excellent	Very poor	UF
5	F	HUS	957	After 2015	KTx+	Good	Very poor	F
6	F	TTP	4380	Pre 2011	KTx+	Very Good	Very poor	MUF
7	F*	HUS	551	2011-2015	KTx+	Very Good	Very poor	F
8	F	TTP	5110	2011-2015	CI	Very Good	Good	MUF
9	F	PTMA	3650	2011-2015	KTx+	Good	Very poor	MUF
10	F	HUS	1095	2011-2015	KTx+	Good	Very poor	F
11	F	PTMA	520	2011-2015	KTx+	Poor	Poor	MUF
12	F	TTP	1436	Pre 2011	KTx-	Good	Very poor	No reply
13	F	PTMA	2190	After 2015	CI	Good	Very Good	F
14	F	TTP	1157	After 2015	Dialysis	Good	Good	MUF
15	F	TTP	1095	2011-2015	KTx+	Good	Poor	UF
16	F	TTP	2555	Pre 2011	KTx+	Very Good	Very poor	MUF
17	F	OTMA	5110	2011-2015	Dialysis	Poor	Good	UF
18	F	PTMA	730	2011-2015	KTx+	Very Good	Very poor	UF
19	F	OTMA	551	After 2015	CI	Very Poor	Good	MUF
20	Other	TTP	2555	Pre 2011	KTx+	Good	Very poor	UF
21	M	TTP	3285	Pre 2011	Dialysis	Poor	Very poor	MUF

*under 18 years OTMA – Other TMA, PTMA – Pregnancy TMA, Ktx -Kidney transplant MF-Most favourable, F- Favourable, UF- Unfavourable, MUF Most Unfavourable

The issue for those aHUS patients misdiagnosed then becomes how quickly would a revised and correct diagnosis be made. Likely revision events may follow a misdiagnosed patient's family member being found to have onset with aHUS. A TMA recurrence particularly during, or following, a kidney transplant operation, or possibly a review of ADAMTS13 baseline recorded results in patients diagnosed in the past. Unless there is a chance event or a systematic and comprehensive medical history revision there remains a possibility that some aHUS patients remain misdiagnosed.

The final question in the study questionnaire sought patients' opinions about what would improve the aHUS diagnosis process. The results are shown in Table 7 below.

Table 7- Patient suggested opportunities for improving the aHUS diagnosis process.

Improvement Opportunity	No.	%	Improvement Opportunity	No.	%
An aHUS specific blood test	147	65	**Understand different causes of TMA**	40	18
Greater awareness of TMA	57	25	**Guidelines available to identify a TMA**	30	13
Speedier transfer between health care providers	54	24	**Awareness of family history of aHUS or kidney disease**	28	12
Greater ability to recognise Acute Kidney Injury	43	19	**Nothing needs to be done**	23	10

Twenty-three patients (10%) were satisfied that nothing needs to be done to improve the process. Some expressed good fortune in their experience by adding comments:

"We were blessed to be in a hospital with doctors who had experience with this disease." "I felt I am considerably lucky because the nephrologist I went to had recently seen another case of aHUS the year before mine." "The hospital where the patient was had a specialist on aHUS, that's why it was recognized so quickly." "I was blessed to be diagnosed as quickly as I was" "We feel lucky to have had a relatively rapid diagnosis" "I was very lucky to have a nephrologist on call that had previously treated a patient with aHUS" "I was extremely lucky that I was in hospital when my kidneys started to fail" "I was very fortunate that haematologist recognised symptoms at an early stage……"

Ninety percent of patients provided at least one suggestion for how the process could be improved. By far the largest response was from 65% of patients who thought that an aHUS specific blood test would help. A speeding up of escalation between providers within the health care systems was suggested by 24% of patients. Other suggestions were mainly about the need for greater awareness and understanding causes of TMA (25%), Acute Kidney Injury (19%) and Family History of aHUS/kidney disease (12%).

Medical education is key to diagnosis process improvement.[56] This is augmented by continued professional development, and deployment of best practices/guidelines and with pooling of knowledge within formal multidisciplinary team health system protocols.[57,58]

CONCLUSION

This study of the aHUS diagnosis process has depended on patients recalling and reporting their authentic experiences and perceptions rather than utilising medical records or other means. It shifts individual anecdotes to a shared portrayal of health care practice at a very difficult time. Collectively, patients say what it is like to go through the process to be diagnosed with the rare disease aHUS.

Patients whose TMA is caused by aHUS can face difficulties in getting an accurate diagnosis. Although there has been improvement post 2011, many patients have still been misdiagnosed, mostly with TTP, and then experience a prolonged delay for the diagnostic error to be revised. Prolongation of accurate diagnosis decision making results in poorer health and treatment burden outcomes and leaves a lasting unfavourable perception of the process.

Around half of patients have experienced a favourable diagnosis timeline, but improvements can still be made through greater awareness of TMAs, education of clinicians, and team-based approaches to recognise, understand and discern each TMA's cause to diagnose aHUS and access effective treatment sooner. Future aHUS patients could then benefit from better health outcomes to match their expectations of health care.

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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.

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