Atypical hemolytic uremic syndrome (aHUS) clinical characteristics associated with renal replacement therapy (RRT) initiation during index hospitalization and RRT requirement after discharge

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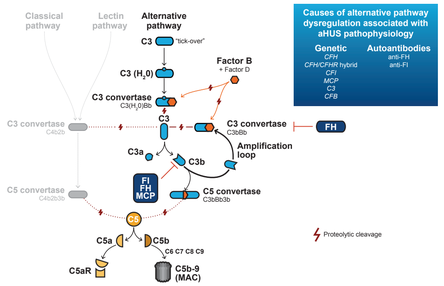
Introduction

- aHUS is a rare, progressive, life-threatening form of TMA with an estimated incidence of 0.2–1.9 per million per year[1–3]
- aHUS is caused by dysregulation of the alternative complement pathway due to genetic abnormalities and/or acquired autoantibodies to complement regulatory proteins (**Figure 1**)[4,5]
- aHUS is associated with risk for kidney failure and/or mortality, with approximately two-thirds of adults progressing to kidney failure or death within 5 years of disease presentation[1,6]
- C5i, such as eculizumab and ravulizumab, have significantly improved clinical outcomes for patients with aHUS[1,7,8]; however, since the introduction of C5i into clinical practice, there has been a lack of large retrospective cohort studies of adults with aHUS in the US
- In this analysis, we present the clinical characteristics and treatment patterns associated with receipt of in-hospital RRT and discontinuation of RRT before the point of discharge in a large, diverse cohort of US adults with presumed incident aHUS treated with C5i

Figure 1. Pathophysiology of aHUS[1,5,9]



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aHUS, atypical hemolytic uremic syndrome; C, complement; FH, factor H; FI, factor I; MAC, membrane attack complex; MCP, membrane cofactor protein; R, receptor.

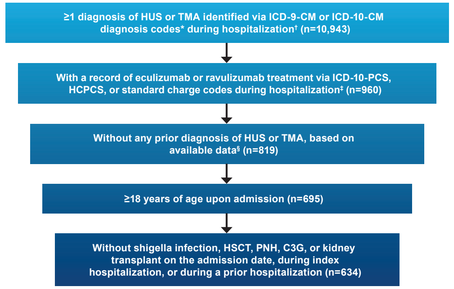
Methods

- This was a retrospective cohort study of adults with EHR in the US Premier Healthcare Database who had a presumed incident diagnosis of aHUS and treatment with eculizumab and/or ravulizumab during hospitalization between January 1, 2011 and June 30, 2021
  - The index date was defined as the date of the first hospitalization for patients meeting the inclusion criteria
  - The index hospitalization period was defined as the time hospitalized for aHUS from the index date to the date of discharge
- aHUS was defined as the presence of a diagnostic code for HUS or TMA and a treatment code for C5i in the absence of a diagnostic code for secondary causes of HUS or TMA or other diseases associated with C5i (**Figure 2**)
  - Included patients were ≥18 years of age upon admission, had ≥1 diagnosis of TMA or HUS during hospitalization (identified via ICD-9-CM or ICD-10-CM), and had a record of eculizumab or ravulizumab treatment during hospitalization (identified via ICD-10-PCS, HCPCS, or standard charge codes)
  - Excluded patients were any with a prior diagnosis of HUS or TMA or any record of shigella infection, HSCT, PNH, C3G, or kidney transplant on the index date, during the index hospitalization period, or during a prior hospitalization
- Demographics and clinical characteristics at the index hospitalization are described, as well as the hospital stay and treatment patterns during the index hospitalization period
- Patients who received in-hospital RRT were compared with those who did not receive in-hospital RRT to determine clinical characteristics and treatment patterns associated with RRT
  - In addition, among patients who received RRT and survived to the point of discharge, those who discontinued before discharge were compared with patients who did not discontinue before discharge to determine clinical characteristics and treatment patterns associated with the ability to discontinue RRT
- For the univariate analysis, continuous variables were summarized by the median and IQR, and analyzed by Wilcoxon signed-rank test or Kruskal–Wallis test; categorical variables were summarized by counts and percentages and analyzed by Fisher's exact test or Chi-square test. Two-sided P-values were reported
- For the multivariable analyses, independent variables were selected based on univariate associations with the outcome (P<0.05). Logistic regression was used to determine the odds ratio of receiving RRT during hospitalization with 95% CIs and P-values

Results

- Among 10,943 patients with ≥1 diagnosis of TMA or HUS during hospitalization in the US Premier Healthcare Database, 634 patients met the criteria for the study (**Figure 2**)

Figure 2. Selection of patients in the US Premier Healthcare Database



*Diagnosis of aHUS was based on the presence of HUS and the absence of shigella infection, HSCT, PNH, C3G, or kidney transplant; as such, there was no unique diagnosis code for aHUS specifically; †Only inpatients were identified, and hospital-based outpatients were excluded at this step; ‡The first hospitalization meeting the first two criteria was the index hospitalization; §For patients with data available on prior hospital encounters, those with previous diagnoses of HUS or TMA were excluded.
aHUS, atypical hemolytic uremic syndrome; C3G, complement 3 glomerulopathy; CM, Clinical Modification; HCPCS, Healthcare Common Procedure Coding System; HSCT, hematopoietic stem cell transplantation; HUS, hemolytic uremic syndrome; ICD, International Classification of Diseases; PCS, Procedure Coding System; PNH, paroxysmal nocturnal hemoglobinuria; TMA, thrombotic microangiopathy; US, United States.

Demographics, clinical characteristics, and duration of RRT

- Data are summarized for the overall population and stratified by (i) receipt of RRT and (ii) discontinuation vs continuation of RRT during the index hospitalization period in **Table 1**
- The majority of patients were female (67.2%), White (61.5%), and non-Hispanic (76.3%), with a median age of 51 years (IQR: 32–64 years)
- Most patients (87.7%) were treated with eculizumab only; ravulizumab monotherapy was received by 9.0% of patients, and 3.3% received both eculizumab and ravulizumab
- Overall, RRT was initiated in 77.3% (490/634) of patients
  - The median time from admission to initiation of RRT was 3 days (IQR: 2–6 days), and the median duration of RRT was 13 days (IQR: 6–22 days)
  - Among those who received RRT, 87.6% (429/490) of patients survived to the point of discharge
  - RRT was discontinued by the point of discharge in 51.3% (220/429) of survivors

Conclusions

- **The preservation of renal function in aHUS remains a challenge, as indicated by a high requirement for RRT described in this real-world US cohort**
- **In the multivariable analysis, RRT during the index hospitalization period was associated with White race, history of heart failure, ICU admission, anemia, and TPE treatment**
- **In the univariate analysis, RRT during the index hospitalization period was also associated with a delay in TPE initiation**
- **For the subgroup of patients who received RRT, RRT at discharge was associated with hypertension, chronic kidney disease, reduced frequency of treatment with TPE or CS, and shorter time to initiation of CS therapy**
- **Future efforts should be made to establish a causal relationship between aHUS treatment delay and RRT, and develop additional precision therapies to reduce renal morbidity in aHUS**

Table 1. Univariate analysis of patient demographics and clinical characteristics associated with RRT

Category	Overall N=634	Received RRT n=490	Received no RRT n=144	P-value*	Discontinued RRT† n=220	Continued RRT† n=208	P-value*
Age, years							
Median (IQR)	51 (32.0–64.0)	51 (32.0–64.0)	52 (30.5–63.0)	0.7735	51 (33.5–64.5)	46 (30.5–59.0)	0.0646
Sex, n (%)							
Female	426 (67.2)	332 (67.8)	94 (65.3)	0.6140	149 (67.7)	136 (65.4)	0.6101
Male	208 (32.8)	158 (32.2)	50 (34.7)		71 (32.3)	72 (34.6)	
Race, n (%)							
White	390 (61.5)	314 (64.1)	76 (52.8)		147 (66.8)	125 (60.1)	
Black	151 (23.8)	114 (23.3)	37 (25.7)		49 (22.3)	54 (26.0)	
Asian	18 (2.8)	12 (2.4)	6 (4.2)	0.0448	3 (1.4)	7 (3.4)	0.5081
Other	62 (9.8)	40 (8.2)	22 (15.3)		17 (7.7)	18 (8.7)	
Unknown	13 (2.1)	10 (2.0)	3 (2.1)		4 (1.8)	4 (1.9)	
Ethnicity, n (%)							
Hispanic	45 (7.1)	32 (6.5)	13 (9.0)		14 (6.4)	12 (5.8)	
Non-Hispanic	484 (76.3)	380 (77.6)	104 (72.2)	0.3540	168 (76.4)	162 (77.9)	0.9203
Unknown	105 (16.6)	78 (15.9)	27 (18.8)		38 (17.3)	34 (16.3)	
Comorbidities at admission, n (%)							
Hypertension	446 (70.3)	352 (71.8)	94 (65.3)	0.1462	146 (66.4)	164 (78.8)	0.0048
Diabetes	114 (18.0)	85 (17.3)	29 (20.1)	0.4597	40 (18.2)	29 (13.9)	0.2401
Heart failure	121 (19.1)	108 (22.0)	13 (9.0)	0.0003	43 (19.5)	44 (21.2)	0.7192
Chronic kidney disease	193 (30.4)	149 (30.4)	44 (30.6)	1.0000	57 (25.9)	76 (36.5)	0.0214
Atrial fibrillation	54 (8.5)	46 (9.4)	8 (5.6)	0.1753	21 (9.5)	10 (4.8)	0.0640
Myocardial infarction	35 (5.5)	27 (5.5)	8 (5.6)	1.0000	8 (3.6)	13 (6.3)	0.2645

*Continuous variables were analyzed by Wilcoxon signed-rank test or Kruskal–Wallis test; categorical variables were analyzed by Fisher's exact test or Chi-square test; †Excludes patients who died during the index hospitalization period and one patient who did not have available service day for RRT.
IQR, interquartile range; RRT, renal replacement therapy.

Clinical characteristics associated with the requirement for RRT during hospitalization in the univariate analysis

- Compared with patients who did not receive RRT, those who initiated RRT were significantly more likely to be White (64.1% vs 52.8%, P=0.0448) and have a history of heart failure (22.0% vs 9.0%, P=0.0003) (**Table 1**)
  - Age, sex, ethnicity, and the presence of hypertension, chronic kidney disease, or diabetes were not significantly associated with receipt of RRT
- The median duration of hospital stay and the median duration of ICU stay were significantly longer for patients who received RRT compared with patients who did not receive RRT (22 vs 16 days, P<0.0001, and 6 vs 4 days, P=0.0006, respectively) (**Table 2**)
  - During the index hospitalization period, thrombocytopenia and anemia were more frequent in patients who received RRT than in those who did not receive RRT (36.9% vs 27.1%, P=0.0290, and 91.2% vs 82.6%, P=0.0055, respectively)
- Compared with those who did not receive RRT, patients receiving in-hospital RRT had a longer delay between admission and initiation of treatment with TPE (3 vs 2 days, P=0.0072) and C5i (10 vs 7 days, P=0.0006), but not CS (2 days for both groups, P=0.0213) (**Table 2**)

Clinical characteristics associated with the requirement for RRT at discharge in the univariate analysis

- Compared with discontinuation of RRT, RRT at discharge was associated with a history of hypertension (78.8% vs 66.4%, P=0.0048) and chronic kidney disease (36.5% vs 25.9%, P=0.0214) but not with age, race, ethnicity, sex, diabetes, or heart failure (**Table 1**)
- Compared with RRT discontinuation, RRT at discharge was associated with reduced frequency of treatment with TPE (65.4% vs 83.6%, P<0.0001) and CS (73.1% vs 81.4%, P=0.0494) (**Table 2**)
  - RRT at discharge was also associated with a shorter median time between admission and initiation of CS (2 vs 3 days, P=0.0014) but not between admission and initiation of C5i (8 vs 10 days, P=0.0565) or TPE (2 vs 3 days, P=0.6937)

Table 2. Univariate analysis of hospital stay and treatment patterns associated with RRT

Category	Overall N=634	Received RRT n=490	Received no RRT n=144	P-value*	Discontinued RRT† n=220	Continued RRT† n=208	P-value*
Type of hospitalization, n (%)‡							
ICU	456 (71.9)	370 (75.5)	86 (59.7)		167 (75.9)	144 (69.2)	
Step-down	96 (15.1)	69 (14.1)	27 (18.8)	0.0004	30 (13.6)	36 (17.3)	0.3115
General ward	82 (12.9)	51 (10.4)	31 (21.5)		23 (10.5)	28 (13.5)	
Duration of hospital stay, days							
Median (IQR)	20 (14.0–32.0)	22 (15.0–33.0)	16 (11.0–27.0)	<0.0001	23 (16.0–35.0)	19 (13.0–27.0)	0.0012
Duration of ICU stay for patients with ICU visit, days							
Median (IQR)	6 (3.0–11.5)	6 (3.0–12.0)	4 (2.0–8.0)	0.0006	7 (3.0–12.0)	5 (2.0–9.0)	0.0046
Comorbidities§ during the index hospitalization period, n (%)							
Malignant hypertension	106 (16.7)	81 (16.5)	25 (17.4)	0.8005	32 (14.5)	43 (20.7)	0.1000
Thrombocytopenia	220 (34.7)	181 (36.9)	39 (27.1)	0.0290	87 (39.5)	72 (34.6)	0.3175
Anemia	566 (89.3)	447 (91.2)	119 (82.6)	0.0055	195 (88.6)	200 (96.2)	0.0036
Cerebrovascular accident	78 (12.3)	58 (11.8)	20 (13.9)	0.5636	24 (10.9)	18 (8.7)	0.5162
Acute kidney injury	560 (88.3)	456 (93.1)	104 (72.2)	<0.0001	198 (90.0)	201 (96.6)	0.0068
Time from admission to treatment with any CSi, days							
Median (IQR)	9 (5.0–15.0)	10 (6.0–16.0)	7 (4.0–13.0)	0.0006	10 (6.0–16.0)	8 (5.0–14.0)	0.0565
Therapeutic plasmapheresis exchange (TPE)							
Patients with TPE, n (%)	438 (69.1)	362 (73.9)	76 (52.8)	<0.0001	184 (83.6)	136 (65.4)	<0.0001
Duration of TPE, days (IQR)	5 (3.0–12.0)	5 (3.0–12.0)	5 (3.0–10.5)	0.7997	6 (3.0–12.0)	5 (2.5–10.5)	0.1636
Time from admission to TPE, days (IQR)	3 (2.0–5.0)	3 (2.0–6.0)	2 (1.0–4.5)	0.0072	3 (2.0–5.0)	2 (2.0–5.0)	0.6937
Corticosteroids (CS)							
Patients with CS, n (%)	498 (78.5)	381 (77.8)	117 (81.3)	0.4195	179 (81.4)	152 (73.1)	0.0494
Duration of CS, days (IQR)	17 (8.0–28.0)	17 (9.0–29.0)	15.5 (6.0–25.5)	0.0990	19 (9.0–29.0)	15 (6.5–23.0)	0.0488
Time from admission to CS, days (IQR)	2 (1.0–5.0)	2 (1.0–5.0)	2 (1.0–4.0)	0.0213	3 (2.0–6.0)	2 (1.0–3.0)	0.0014

Duration of treatment and time from admission to treatment are expressed as median (IQR).
*Continuous variables were analyzed by Wilcoxon signed-rank test or Kruskal–Wallis test; categorical variables were analyzed by Fisher's exact test or Chi-square test; †Excludes patients who died during the index hospitalization period and one patient who did not have available service day for RRT; ‡Patients with ICU and step-down are mutually exclusive. Patients with both ICU and step-down are bucketed under ICU. General ward should not have both ICU and step-down during hospitalization; §Microangiopathic hemolytic anemia and renal failure are not included.
C5i, C5 inhibitor therapy; CS, corticosteroids; ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy; TPE, therapeutic plasmapheresis exchange.

Risk factors at index hospitalization associated with RRT

- In a multivariable analysis (**Table 3**), the odds of in-hospital mortality were more than two-times greater among patients who were admitted to the ICU (P=0.002), had anemia (P=0.016) or heart failure (P=0.003), or received TPE (P=0.012)
  - The odds of RRT were also approximately halved among White race vs other race (P=0.011)

Table 3. Multivariable analysis of risk factors at index hospitalization associated with RRT

Covariate	Odds ratio	95% CI	P-value
Race			
Black vs White	0.75	0.45–1.25	0.271
Other vs White	0.48	0.27–0.84	0.011
ICU admission	2.07	1.31–3.26	0.002
Duration of hospitalization	1.01	0.99–1.02	0.331
Time from admission to any C5i, days	1.01	0.99–1.04	0.329
Anemia	2.11	1.15–3.87	0.016
Heart failure	2.69	1.40–5.15	0.003
Received both corticosteroids + TPE	0.85	0.42–1.71	0.649
Received TPE	2.47	1.22–5.03	0.012
Thrombocytopenia	1.53	0.97–2.42	0.067

The multivariable model was also adjusted for region, hospital teaching status, location, and bed size.
CSi, C5 inhibitor therapy; CI, confidence interval; ICU, intensive care unit; RRT, renal replacement therapy; TPE, therapeutic plasmapheresis exchange.

Limitations

- As with all EHR-based studies, the diagnosis codes and data recorded in the database may be subject to human or technical error or data omission
- Since aHUS is largely a diagnosis of exclusion, it is possible that a small number of patients received an alternative TMA diagnosis after discharge, and C5i was, therefore, discontinued
- Due to the EHR nature of the database, it was not possible to include a baseline period; therefore, prevalent cases of aHUS may have been included in the study population
- As ravulizumab is a newer therapy, most patients received eculizumab during the study period. This limited stratification of results by treatment type
- The time from admission to, and duration of, TPE and CS variables were not included in the multivariable model as not all patients were exposed to these interventions
- The results from this study may not be generalizable to other populations beyond those identified in the database

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Abbreviations

aHUS, atypical hemolytic uremic syndrome; C, complement; C3G, complement 3 glomerulopathy; C5i, C5 inhibitor therapy; CI, confidence interval; CM, Clinical Modification; CS, corticosteroids; EHR, electronic health records; FH, factor H; FI, factor I; HCPCS, Healthcare Common Procedure Coding System; HSCT, hematopoietic stem cell transplantation; HUS, hemolytic uremic syndrome; ICD, International Classification of Diseases; ICU, intensive care unit; IQR, interquartile range; MAC, membrane attack complex; MCP, membrane cofactor protein; PCS, Procedure Coding System; PNH, paroxysmal nocturnal hemoglobinuria; R, receptor; RRT, renal replacement therapy; TMA, thrombotic microangiopathy; TPE, therapeutic plasmapheresis exchange; US, United States.

Disclosures

SO, **BN**, and **JN** are employees of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA. **EN**, **CNM**, and **SS** are employees of Genesis Research LLC, Hoboken, New Jersey, USA.

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