Atypical hemolytic uremic syndrome (aHUS) clinical characteristics and treatment patterns associated with mortality during index hospitalization

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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 ravulizumab and eculizumab, 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 in-hospital mortality in a large, diverse cohort of US adults with presumed incident aHUS treated with C5i

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

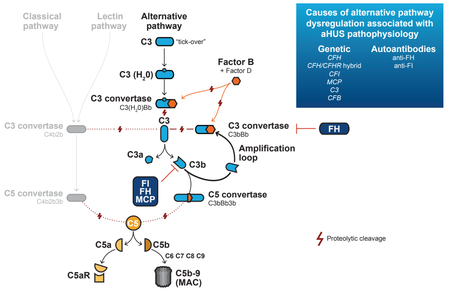


Figure adapted under the CC BY 4.0 license from Tesař V et al. *Kidney Int Rep*. 2023;8:1730–1740.
aHUS, atypical hemolytic uremic syndrome; C, complement; FH, factor H; FI, factor I; MAC, membrane attack complex; MCP, membrane cofactor protein; R, receptor.

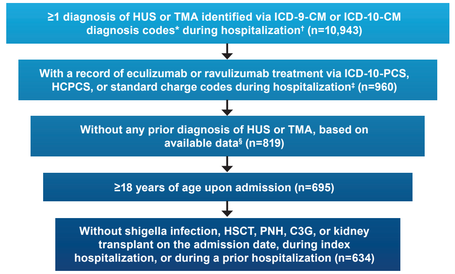
Methods

- 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 HUS or TMA 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, treatment patterns, and mortality during the index hospitalization period
- Patients who died during hospitalization were compared with those who were alive at the point of discharge to determine risk factors associated with in-hospital mortality
- For the univariate analysis, continuous variables were summarized by 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 in-hospital mortality 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.

Conclusions

- **Using multivariable analysis, increased in-hospital mortality in patients with presumed incident aHUS was associated with older age, ICU admission, cerebrovascular accident, and time from admission to C5i initiation**
- **In the univariate analysis, in-hospital mortality was also associated with older age, delayed initiation of TPE and RRT, prolonged exposure to CS, and delayed time from C5i initiation to CS discontinuation**
- **Future efforts should focus on the development of prognostic risk calculators, reducing treatment delays, and the development of more targeted, steroid-sparing treatments**

Demographics and clinical characteristics

- Data are summarized for the overall population and stratified by in-hospital mortality in **Table 1**
- Most 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, 78 patients (12.3%) died during the index hospitalization
- Among 285 patients (45.0%) with mortality data post-discharge, 30-day and 365-day mortality rates were 3.5% and 8.8%, respectively

Clinical characteristics and treatment patterns associated with mortality during index hospitalization in the univariate analysis

- In-hospital mortality was associated with an older median age (63 vs 49 years, P<0.0001), and a history of diabetes (29.5% vs 16.4%, P=0.0072), heart failure (30.8% vs 17.4%, P=0.0083), or atrial fibrillation (21.8% vs 6.7%, P<0.0001) (**Table 1**)
- Compared with those who were alive at the point of discharge, patients who died during hospitalization had a longer median hospital stay (31 vs 20 days, P<0.0001) (**Table 2**)
  - Among patients with an ICU visit (71.9%), in-hospital mortality was associated with a longer median ICU stay vs patients who were alive at the point of discharge (14 vs 5 days, P<0.0001)
  - Cerebrovascular accident during the index hospitalization was more frequent among patients who died compared with those who survived to discharge (26.9% vs 10.3%, P=0.0001)
- Patients who died during hospitalization experienced a longer median delay between admission and initiation of TPE (5 vs 2 days, P<0.0001) or any C5i (15 vs 8 days, P<0.0001) (**Table 2**)
- Although not associated with exposure or time to initiation of treatment with CS, in- hospital mortality was associated with duration of CS use (27 vs 16 days, P<0.0001) and time from C5i initiation to CS discontinuation (14 vs 6 days, P=0.0156) (**Table 2**)
- In-hospital mortality was also associated with a longer median time to RRT (5 vs 3 days, P<0.0001) and increased duration of RRT (18 vs 13 days, P=0.0241) (**Table 2**)

Table 1. Univariate analysis of patient demographics and clinical characteristics associated with in-hospital mortality during the index hospitalization period

Category	Overall N=634	Died during hospitalization n=78	Alive at the point of discharge n=556	P-value*
Age, years				
Median (IQR)	51 (32.0–64.0)	63 (47.0–71.0)	49 (31.0–62.0)	<0.0001
Sex, n (%)				
Female	426 (67.2)	54 (69.2)	372 (66.9)	0.7969
Male	208 (32.8)	24 (30.8)	184 (33.1)	
Race, n (%)				
White	390 (61.5)	50 (64.1)	340 (61.2)	
Black	151 (23.8)	16 (20.5)	135 (24.3)	
Asian	18 (2.8)	2 (2.6)	16 (2.9)	0.9247
Other	62 (9.8)	8 (10.3)	54 (9.7)	
Unknown	13 (2.1)	2 (2.6)	11 (2.0)	
Ethnicity, n (%)				
Hispanic	45 (7.1)	5 (6.4)	40 (7.2)	
Non-Hispanic	484 (76.3)	64 (82.1)	420 (75.5)	0.4354
Unknown	105 (16.6)	9 (11.5)	96 (17.3)	
Comorbidities at admission, n (%)				
Hypertension	446 (70.3)	52 (66.7)	394 (70.9)	0.5081
Diabetes	114 (18.0)	23 (29.5)	91 (16.4)	0.0072
Heart failure	121 (19.1)	24 (30.8)	97 (17.4)	0.0083
Chronic kidney disease	193 (30.4)	21 (26.9)	172 (30.9)	0.5134
Atrial fibrillation	54 (8.5)	17 (21.8)	37 (6.7)	<0.0001
Myocardial infarction	35 (5.5)	7 (9.0)	28 (5.0)	0.1800

*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.
IQR, interquartile range.

Table 2. Univariate analysis of hospital stay and treatment patterns associated with in-hospital mortality during the index hospitalization period

Category	Overall N=634	Died during hospitalization n=78	Alive at the point of discharge n=556	P-value*
Type of hospitalization, n (%)†				

Risk factors associated with mortality during index hospitalization

- In a multivariable analysis (**Table 3**), the odds of in-hospital mortality were approximately 6.8 times greater among patients admitted to the ICU (P<0.001) and 3.0 times greater among those with cerebrovascular accident (P=0.001)
  - In-hospital mortality was also associated with age (P=0.005) and time from admission to any C5i (P=0.010)

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, RRT, 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**, **AB**, and **DG** are employees of Genesis Research LLC, Hoboken, New Jersey, USA.

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