Atypical hemolytic uremic syndrome (aHUS) clinical characteristics and outcomes during index hospitalization diagnosis in the era of C5 inhibitor therapy (C5i)

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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 complement alternative pathway due to genetic abnormalities and/or acquired autoantibodies to complement regulatory proteins[4,5]
- aHUS is associated with end-organ damage, including kidney failure and/or mortality[1,6]
  - Approximately two-thirds of adults progress to kidney failure or death within 5 years of disease presentation[1,7]
- C5i, such as eculizumab and ravulizumab, have significantly improved clinical outcomes for patients with aHUS[1,8,9]; 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 clinical characteristics, treatment patterns, and outcomes in a large, diverse cohort of US adults with presumed incident aHUS treated with C5i in an inpatient setting

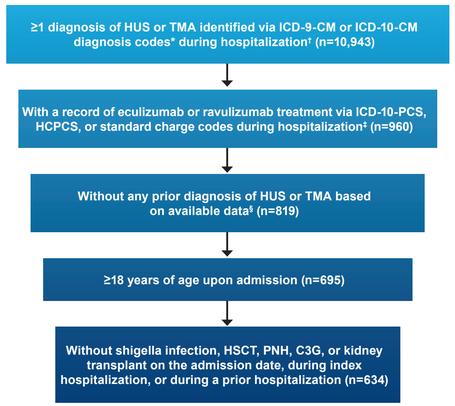
Methods

- 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 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 1**)
  - 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 index hospitalization are described, as well as the patient journey, clinical outcomes, and treatment patterns during the index hospitalization period. Clinical and outcomes data were analyzed using descriptive statistics
  - Continuous variables were summarized by the median and IQR
  - Categorical variables were summarized by counts and percentages

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 1**)

Figure 1. 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 and clinical characteristics

- Demographic and clinical characteristic data are summarized 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)
- Overall, the most frequent comorbidities included hypertension (70.3%), chronic kidney disease (30.4%), heart failure (19.1%), and diabetes (18.0%)
- Most patients were admitted to hospitals in the Southern US (49.8%), in urban centers (92.6%), and to hospitals that were teaching institutions (65.6%) (**Table 2**)

Patient journey, treatment patterns, and clinical outcomes

- Patient journey, treatment patterns, and mortality data are summarized in **Table 3**
- The median duration of hospital stay was 20 days (IQR: 14–32 days)
  - Among patients with an ICU visit (71.9%), the median duration of ICU stay was 6 days (IQR: 3–12 days)
- The median time from admission to treatment with any C5i was 9 days (IQR: 5–15 days), and 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
- The median time from admission to treatment with CS or TPE was 2 days (IQR: 1–5 days) and 3 days (IQR: 2–5 days), respectively
  - Overall, 78.5% of patients received CS, and 69.1% received TPE
  - The median treatment duration for patients receiving CS, or TPE, was 17 days (IQR: 8–28 days) and 5 days (IQR: 3–12 days), respectively
- RRT was initiated in 77.3% of patients; among those who survived to the point of discharge (n=429), RRT was discontinued prior to discharge in 51.3%
  - 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)
- The most frequent comorbidities during the index hospitalization period were anemia (89.3%) and acute kidney injury (88.3%)
- In-hospital mortality was 12.3%, and 22.7% of patients required follow-up in skilled care facilities

Conclusions

- **Despite the substantial clinical benefits from C5i, aHUS remains a morbid disease, as indicated by hospital and ICU stay duration, receipt of RRT, discharge care requirements, and mortality described in this real-world US cohort**
- **Future efforts should focus on the development of prognostic risk calculators, improved time to treatment, and the development of novel therapies**

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
- The results from this study may not be generalizable to other populations beyond those identified in the database

Table 1. Demographics and clinical characteristics of patients with aHUS at admission of index hospitalization

Category	Overall (N=634)
Age, years (IQR)	
Median age	51 (32.0–64.0)
Sex, n (%)	
Female	426 (67.2)
Male	208 (32.8)
Race, n (%)	
White	390 (61.5)
Black	151 (23.8)
Asian	18 (2.8)
Other	62 (9.8)
Unknown	13 (2.1)
Ethnicity, n (%)	
Hispanic	45 (7.1)
Non-Hispanic	484 (76.3)
Unknown	105 (16.6)
Comorbidities at admission, n (%)	
Hypertension	446 (70.3)
Diabetes	114 (18.0)
Heart failure	121 (19.1)
Chronic kidney disease	193 (30.4)
Atrial fibrillation	54 (8.5)
Myocardial infarction	35 (5.5)
Insurance type, n (%)	
Medicare	203 (32.0)
Medicaid	163 (25.7)
Managed care	164 (25.9)
Commercial	60 (9.5)
Self-pay	22 (3.5)
Other	22 (3.5)

IQR, interquartile range.

Table 2. Hospital details for included patients admitted for aHUS

Category	Overall (N=634)
Region, n (%)	
Midwest	93 (14.7)
Northeast	131 (20.7)
South	316 (49.8)
West	94 (14.8)
Location, n (%)	
Rural	47 (7.4)
Urban	587 (92.6)
Teaching status, n (%)	
No	218 (34.4)
Yes	416 (65.6)
Bed size, n (%)	
000–099	1 (0.2)
100–199	26 (4.1)
200–299	62 (9.8)
300–399	93 (14.7)
400–499	81 (12.8)
≥500	371 (58.5)

Table 3. Patient journey, treatment patterns, and clinical outcomes of patients with aHUS during the index hospitalization period

Category	Overall (N=634)
Type of hospitalization, n (%)*	
ICU	456 (71.9)
Step-down	96 (15.1)
General ward	82 (12.9)
Duration of hospital stay, days	
Median (IQR)	20 (14.0–32.0)
Duration of ICU stay for patients with ICU visit, days	
Median (IQR)	6 (3.0–11.5)
Time from admission to treatment with any C5i, days	
Median (IQR)	9 (5.0–15.0)
Therapeutic plasmapheresis exchange (TPE)	
Patients with TPE, n (%)	438 (69.1)
Duration of TPE, days (IQR)	5 (3.0–12.0)
Time from admission to TPE, days (IQR)	3 (2.0–5.0)
Fresh frozen plasma (FFP)	
Patients with FFP, n (%)	473 (74.6)
Duration of FFP, days (IQR)	6 (3.0–11.0)
Time from admission to FFP, days (IQR)	3 (1.0–6.0)
Corticosteroids (CS)	
Patients with CS, n (%)	498 (78.5)
Duration of CS, days (IQR)	17 (8.0–28.0)
Time from admission to CS, days (IQR)	2 (1.0–5.0)
Renal replacement therapy (RRT)	
Patients with RRT, n (%)	490 (77.3)
Duration of RRT, days (IQR)	13 (6.0–22.0)
Time from admission to RRT, days (IQR)	3 (2.0–6.0)
Patients with RRT who survived to discharge	429 (87.6)
Patients discontinuing RRT before discharge, n (%)†	220 (51.3)
Comorbidities‡ during the index hospitalization period, n (%)	
Malignant hypertension	106 (16.7)
Thrombocytopenia	220 (34.7)
Anemia	566 (89.3)
Cerebrovascular accident	78 (12.3)
Acute kidney injury	560 (88.3)
In-hospital mortality, n (%)	
Patients with in-hospital mortality	78 (12.3)

Duration of treatment and time from admission to treatment are expressed as median (IQR).
*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; †Percentage expressed as the proportion of patients with RRT who survived to discharge (n=429; excludes patients who died during index hospitalization); ‡Microangiopathic hemolytic anemia and renal failure are not included.
C5i, C5 inhibitor therapy; ICU, intensive care unit; IQR, interquartile range.

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Abbreviations

aHUS, atypical hemolytic uremic syndrome; C3G, complement 3 glomerulopathy; C5i, C5 inhibitor therapy; CM, Clinical Modification; CS, corticosteroids; EHR, electronic health records; FFP, fresh frozen plasma; 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; PCS, Procedure Coding System; PNH, paroxysmal nocturnal hemoglobinuria; RRT, renal replacement therapy; TMA, thrombotic microangiopathy; TPE, therapeutic plasmapheresis exchange; US, United States.

Disclosures

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