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EXPERT OPINION

Research Gaps and Priorities for aHUS in the Gulf Cooperation Countries (GCC): Findings from a Payer-Focused Expert Meeting

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Abstract: Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening complement-mediated thrombotic microangiopathy (TMA) associated with high morbidity, mortality, and substantial healthcare resource utilization (HCRU). Although complement inhibitors such as eculizumab and ravulizumab have dramatically improved outcomes, aHUS continues to impose significant economic and operational burden on healthcare systems. In the Gulf region, payers and health systems face increasing pressures driven by rising costs, delayed diagnosis, fragmented access, and limited real-world evidence necessary for informed resource allocation decisions. This manuscript summarizes the findings of a payer-focused regional expert meeting, which included three presentations: (1) the role and value of HCRU studies for payers, (2) the clinical and economic burden of aHUS, and (3) existing global evidence on HCRU in aHUS and gaps relevant to the Gulf. The meeting concluded with an expert panel discussion and a survey assessing feasibility and priorities for a collaborative real-world study. Consensus highlighted urgent needs to establish regional incidence and prevalence, quantify utilization and cost burden, evaluate treatment patterns and outcomes, and design a standardized multicenter study. Priority research directions include retrospective chart review with prospective follow-up and unified data collection across Gulf institutions. These findings provide a payer-informed roadmap for building evidence that can support sustainable, equitable, and value-based decision making for aHUS care in the region.

Keywords: rare diseases, reimbursement, health technology assessment, formulary, orphan drugs, aHUS, research gaps, Gulf

Introduction

Healthcare systems globally are experiencing unprecedented financial and operational pressures driven by an aging population, increased chronic disease burden, and rapid development of advanced and high-cost therapeutic innovations. Rare diseases pose particular challenges because of delayed and complex diagnosis, multisystem involvement, limited evidence, and significant direct and indirect costs. In the GCC region—characterized by fast population growth, high rates of consanguinity, and expansion of access to specialty therapy—the economic and ethical tensions surrounding rare diseases are amplified.[1,2]

Atypical hemolytic uremic syndrome (aHUS) is a complement-mediated thrombotic microangiopathy characterized by systemic endothelial injury, thrombocytopenia, microangiopathic hemolytic anemia, and progressive organ dysfunction, most commonly affecting renal vasculature.[3] Without treatment, up to 50% of patients progress to end-stage renal disease (ESRD) after the first aHUS episode, with mortality higher in pediatric patients.[4] The global incidence is between

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0.23–1.9 per million population annually, and prevalence is estimated at approximately 2–9 per million.[5] Regionally, data from Iran suggest significantly higher rates 27.88 per million, raising questions regarding true disease burden in the broader Middle East.[6]

Diagnosis is challenging due to overlapping differential diagnoses, lack of rapid biomarkers, and reliance on exclusion of other etiologies of TMAs, such thrombotic thrombocytopenic purpura (TTP), Shiga-toxin mediated HUS, malignancy-related TMA, and drug-induced TMA.[7] Extensive laboratory evaluation and delay in clinical confirmation may postpone treatment initiation, worsening renal and systemic injury.[8]

Complement inhibitors (eculizumab and ravulizumab) introduced since 2011 dramatically improved survival and renal outcomes, but access, affordability, and diagnostic delays remain major challenges.[9,10] With lifelong treatment costs, evidence for real-world resource utilization is essential for reimbursement, budget forecasting, and resource planning.

In the GCC region, healthcare systems are predominantly government funded, and payers play a central role in determining access to high-cost therapies through formulary decisions and reimbursement policies. Rare diseases such as aHUS therefore present significant policy challenges due to limited epidemiological data, fragmented health information systems, and uncertainty surrounding long-term treatment costs. Despite these challenges, no studies from the GCC region evaluate the epidemiology, utilization, costs, or outcomes in aHUS.

For regional payers responsible for resource allocation, real-world HCRU data are essential to justify investment, forecast spending, and support policy and reimbursement decisions. To address this knowledge gap, a regional expert meeting was convened to identify key evidence gaps and define research priorities related to aHUS in the GCC region. This manuscript summarizes the outcomes of that meeting and outlines a payer-informed roadmap for future evidence generation.

Methods

Study Design

This study reports the outcomes of a regional expert meeting designed to identify research priorities and evidence gaps related to atypical hemolytic uremic syndrome (aHUS) in the Gulf Cooperation Council region.

The meeting was structured as a policy-focused expert consultation combining presentations, moderated discussion, and a structured survey of participating institutions.

The objective was to generate informed expert perspectives on research priorities and evaluate the feasibility of collaborative real-world evidence generation across GCC healthcare systems.

Participant Selection

Participants were invited based on expertise in healthcare policy, health technology assessment (HTA), health economics and outcomes research (HEOR), nephrology, and rare disease management.

Experts represented institutions involved in payer decision-making, formulary management, or clinical management of aHUS within GCC healthcare systems.

Participants were drawn from four GCC countries: Saudi Arabia, United Arab Emirates, Kuwait, Bahrain, Qatar and Oman.

Meeting Structure

The meeting consisted of three structured presentations followed by a moderated expert panel discussion.

The presentations addressed:

1. Importance of resource utilization evidence for rare disease decision-making.
2. Clinical and economic burden of aHUS, including diagnostic challenges, organ involvement, and treatment burden.
3. Summary of current evidence on real-world healthcare utilization and cost outcomes.

Following these presentations, a moderated discussion explored evidence gaps, research priorities, and potential approaches for generating regional real-world evidence.

Survey

A structured survey was administered to participating institutions to assess feasibility of conducting a multicenter real-world study.

The survey assessed:

- Institutional case volume
- Availability of electronic health record data
- Access to complement diagnostics and genetic testing
- Feasibility of retrospective chart review
- Priority research questions

Survey responses were summarized descriptively.

Identification of Research Priorities

Research priorities were identified through thematic analysis of expert discussion and survey responses.

Because the meeting aimed to identify exploratory research priorities rather than establish formal consensus recommendations, a formal consensus methodology such as Delphi or nominal group technique was not applied.

Instead, research priorities were identified based on recurring themes emerging across participants.

Results

Evidence Gaps Identified Through Literature Review

The literature review of published HCRU studies showed that most available evidence originates from the United States and Europe. These studies typically evaluate outcomes associated with complement inhibitor therapy and consistently demonstrate reductions in healthcare costs and resource utilization, particularly when treatment is initiated early.[8,11,12]

Ryan et al reported that early initiation of eculizumab (within seven days) was associated with reduced hospital costs, shorter length of stay, and lower mortality, suggesting that diagnostic delays contribute directly to increased healthcare burden.[11] Similarly, Wang et al reported reductions in inpatient and outpatient healthcare utilization following a switch from eculizumab to ravulizumab, with reduced infusion frequency identified as a major contributor to improved resource utilization and patient convenience.[8]

However, these studies were conducted in North American healthcare systems and relied primarily on administrative claims databases. Their findings may therefore not fully reflect the organization, payer structures, and care pathways of GCC healthcare systems.

A further limitation of the existing literature is the lack of long-term follow-up data. Most studies focus on short-term hospitalization outcomes rather than long-term survival, renal recovery, relapse rates, treatment discontinuation strategies, or quality-adjusted life years (QALYs). The absence of societal cost considerations—such as caregiver burden, productivity loss, and psychological impact—also limits comprehensive economic evaluation.[13]

Based on the literature review, several key evidence gaps were identified:

- Absence of epidemiological studies from GCC countries
- Lack of chart-level clinical datasets
- Limited evaluation of long-term clinical outcomes
- Minimal inclusion of societal and indirect costs
- Limited generalizability of existing international data
- Unknown regional prevalence, limiting healthcare planning and reimbursement forecasting

Expert Panel Perspectives

During the expert roundtable, participants emphasized that the burden of aHUS begins at the diagnostic stage, which requires extensive testing and exclusion of multiple differential diagnoses including thrombotic thrombocytopenic purpura (TTP), Shiga toxin–associated HUS, autoimmune etiologies, and drug-induced thrombotic microangiopathy.

Experts highlighted that patients often experience multi-organ involvement, most commonly affecting renal function. Acute kidney injury occurs in approximately 60–70% of patients, with up to 50% progressing to end-stage renal disease if untreated. Cardiovascular, pulmonary, neurological, dermatologic, gastrointestinal, and ocular complications were also discussed as contributors to disease burden and healthcare utilization.[8]

Participants also emphasized the significant treatment burden associated with aHUS, including therapeutic plasma exchange, dialysis, prolonged hospitalization, intensive care unit admissions, vaccination requirements, and complex long-term monitoring.[14–16] Early initiation of complement inhibitor therapy has been associated with reduced hospital length of stay and improved outcomes. However, diagnostic delays remain common, particularly in pregnancy-associated aHUS where clinical presentations may overlap with other conditions.[11,17]

Experts noted that although complement inhibitors have transformed the natural history of aHUS, lifelong treatment costs remain substantial and optimal discontinuation strategies remain uncertain. Evidence suggesting a risk of disease relapse further underscores the need for long-term real-world data.[18–20]

Key Themes Emerging from the Expert Discussion Included

- The need to reduce diagnostic delays through clinician education
- Improved access to complement testing and genetic diagnostics
- Increasing financial pressure associated with current and pipeline therapies
- The need for clinically and payer-aligned criteria for treatment initiation and discontinuation
- Development of a GCC-wide aHUS research collaboration
- Generation of regional real-world evidence to support sustainable reimbursement decisions

Survey Findings on Research Feasibility

Survey responses from participating institutions indicated that collaborative real-world research is feasible across the GCC region.

Participants reported limited case volumes at individual centers and fragmented availability of historical data. Electronic health records were identified as the primary potential data source, as claims databases are not widely used in GCC healthcare systems.

Institutions also reported variable access to therapeutic plasma exchange, complement diagnostics, and genetic testing. Despite these differences, respondents expressed strong support for a multicenter retrospective chart review study covering approximately three to five years of historical data with 12–24 months of follow-up.

The most commonly proposed index date for study inclusion was either the first complement inhibitor dose or the first qualifying coded diagnosis.

Priority Research Areas

Based on the literature review, expert discussion, and survey responses, several priority research areas were identified:

- Regional incidence and prevalence of aHUS
- Diagnostic pathways and time to treatment initiation
- Clinical outcomes including renal recovery, relapse rates, and survival
- Healthcare resource utilization and cost burden including ICU admissions, dialysis, pharmacotherapy, and supportive care
- Pregnancy-associated aHUS

Preferred Study Design

Experts agreed that a multicenter hybrid observational study would represent the most feasible approach to address these evidence gaps.

The proposed framework includes retrospective chart review to establish baseline epidemiology, treatment patterns, and healthcare utilization, combined with prospective follow-up to capture longer-term outcomes.

Standardized data definitions and harmonized data collection across participating institutions were identified as essential to enable meaningful comparison of outcomes across GCC healthcare systems.

Discussion

Rare diseases carry disproportionately high resource use, often three to five times higher than common diseases, increasing financial strain on healthcare systems. Payers must balance ethical obligations to treat all patients with economic realities and opportunity costs, highlighting the need for real data to support value-based decisions.

The findings of this regional expert meeting underscore a substantial gap in real-world evidence related to aHUS in the Gulf region, particularly regarding healthcare utilization, resource burden, diagnostic pathways, and long-term outcomes. While complement inhibition has dramatically improved clinical outcomes, the magnitude of clinical and economic benefit remains insufficiently quantified outside of North American and European datasets. The scarcity of regional data mirrors observations from recent international reviews, which emphasize the need for locally relevant evidence to guide reimbursement and access decisions in rare diseases.[5,8]

From a policy perspective, the lack of regional epidemiologic estimates represents a major obstacle for rational reimbursement planning. Budget impact forecasting for a lifelong therapy such as eculizumab or ravulizumab requires reliable incidence, prevalence, and survival expectations. As highlighted in this meeting, and by Zakzuk Jet al even small inaccuracies can result in significant misalignment in national forecasting due to the rare nature of the disease[21] This challenge is exacerbated in the Gulf, where population demographics include large expatriate populations and variable access pathways across governmental, military, and private sectors.[1,2]

Decision-making for rare diseases increasingly requires real-world evidence to complement clinical trial results, a trend reinforced by regulatory frameworks such as the EMA's adaptive pathways and the SFDA's expanding expectations for economic evaluation. International guidance, including from NICE and CADTH, has emphasized the importance of collecting real-world evidence post-approval to inform access agreements, risk-sharing models, and managed entry programs.[22,23] For example, NICE mandated a prospective study (SETS aHUS) to evaluate eculizumab discontinuation strategies as part of its reimbursement agreement.[24] Similar models may be applicable in the Gulf, where uncertainty surrounding optimal treatment duration represents a major policy and budget concern.

The meeting discussions highlighted an urgent need to quantify local diagnostic delays, access-to-therapy timelines, and treatment variation, reflecting a systems-level performance opportunity. Establishing regional performance indicators may support value-based contracting frameworks and inform proposals to expand complement and genetic testing availability.

The consensus around initiating a multicenter retrospective chart review represents an important step toward building a regional evidence base. Longitudinal observational registries may follow, providing an infrastructure comparable to international efforts such as the Global aHUS Registry. Participation in global registries, currently absent for all Gulf countries, would also strengthen regional research output, address knowledge gaps in pediatric and pregnancy-associated aHUS, and align local practice with global standards.

Several limitations should be acknowledged. First, the findings reflect perspectives from a limited number of experts representing selected institutions and may not fully represent all GCC healthcare systems, especially as representatives from Qatar and Oman apologized and did not attend the meeting. Second, the meeting-based format relied on expert discussion rather than formal consensus methodology or primary empirical data collection. Despite these limitations, the meeting provides an important initial step toward identifying regional research priorities.

Conclusion

This payer-focused regional meeting identified critical evidence gaps in incidence, prevalence, healthcare resource utilization, and treatment outcomes for aHUS in the Gulf region. The absence of real-world data hinders informed

policy, budget planning, and equitable patient access to lifesaving therapy. Consensus support for a multicenter hybrid cohort study provides a clear roadmap to produce meaningful evidence aligned with payer needs and clinical realities. A coordinated regional effort is essential to achieve sustainable rare disease management, reduce diagnostic and treatment delays, and improve outcomes for patients with aHUS.

Operationalizing this research agenda will require coordinated collaboration across regional institutions. Key next steps include establishing a governance structure for multicenter data collection, identifying potential funding mechanisms, and developing standardized data definitions to enable comparability across healthcare systems. Such efforts could also facilitate participation in international initiatives such as the Global aHUS Registry and strengthen regional research capacity in rare diseases.

These findings should be interpreted in the context of the meeting-based methodology and the limited number of participating experts. Nevertheless, the priorities identified provide a practical roadmap for generating the evidence needed to support sustainable and value-based decision making for aHUS care in the region.

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