

PATIENT-CENTRIC APPROACHES IN HEALTH TECHNOLOGY ASSESSMENT FOR ATYPICAL HEMOLYTIC UREMIC SYNDROME-CHALLENGES AND INNOVATIONS

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ABSTRACT

Atypical Hemolytic Uremic Syndrome (aHUS) is a rare, life-threatening condition which is significantly heterogeneous, further burdening patients. Health Technology Assessment (HTA) is important for assessing access to new and innovative therapies for patients with aHUS, but patients are not always involved in the HTA process and, when involved, are frequently tokenized. In this review, we present the extent and involvement of patients in aHUS HTA. We outline systemic limitations including limited involvement of patients, poor transparency, limited resources, and inconsistent data collection methods. We demonstrate the necessity of patients' involvement and perspectives to appropriately capture lived experiences, unmet need, informing outcomes using patient reported outcomes (PROs), and understanding relative impacts on societal level. We suggest practical solutions such as improvements in transparency, advocacy group support, striving to have representation from diverse groups, integrating and developing patient registries and understanding the gaps in culture and language. To expand upon patient engagement, we consider the innovative possibilities of organ-on-chip technologies. Hence creating and enabling personalized modelling of diseases and testing of patient-specific treatments and therapies. This is a new opportunity for patients to engage in research and HTA. We present a case study and suggested the next steps and ultimately advocate for a patient-centered approach to HTAs.

1. INTRODUCTION

Atypical Hemolytic Uremic Syndrome (aHUS) is a rare, chronic condition that is also life-threatening. aHUS is caused by abnormal dysregulation of the complement system, which causes microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. aHUS is estimated to be omnipresent at a rate of 1-2 cases per million each year. Consequently, aHUS creates unique challenges to patients,

clinicians, and policymakers [1]. Health Technology Assessments (HTA) are a key process in evaluating the clinical and economic value of therapies; however, HTA is even more critical for rarer diseases known for producing abnormal burden of disease on patients and extreme costs like aHUS with its need for high-cost treatment of complement inhibitors (eculizumab) and other interventions. The integration of patients' voices in this given HTA process

and activity remains limited and it limits the full potential of understanding the complete burden of disease which can inform equitable access. Therefore, this review delineates the current landscape of patient's influences on aHUS HTAs, comes up with key practical challenges, and presents real change strategies and solutions to enhance patient-centricity. It also considers the emerging world of organ-on-a-chip technology as a potential personalized medicine innovation and map path for HTA evaluations [2]. In conclusion, addressing systemic barriers and leveraging innovation and technology, this article hopes to introduce new ways of thinking about HTA and potential reform in terms of aHUS.

2. BACKGROUND: AHUS AND HTA

2.1 Background of aHUS

Atypical Hemolytic Uremic Syndrome is a difficult clinical disorder of genetic or acquired dysfunction of the complement system resulting in systemic endotheliopathy and multi-organ dysfunction of varying severity and some 'attenuated' chronic forms. All aHUS patients experience recurrent disease phenomena, for example hemolytic anemia, thrombosis and end-organ dysfunction, that carry considerable consequences for quality of life (QoL) [3]. There are interventions, principally eculizumab and rovelizumab, that improve the lives of aHUS patients. However, the costs associated with these therapies mean assessments by Health Technology Assessment (HTA) agencies generate health and economic implications to consider prior to reimbursement decisions.

2.2 The role of HTA

Health technology assessment is a multidisciplinary process assessing and evaluating the clinical and economic value of health technologies, in addition to

societal effects to inform reimbursement and access decisions. Due to factors such as a limited body of evidence, small and heterogeneous patient populations, and high costs of treatment, HTA considers scarce data when balancing the costs of interventions with the value they produce is more challenging for patients with orphan diseases, rare diseases or ultra-rare diseases. Patient engagement is progressively perceived as an essential part of HTA to ensure the applicants publicly funded and reimbursement growth engagement can be validated while depicting the individual and societal burden through patient narrative evidence when initiatives in HTA appear one-sided or driven by institutions with competitive economic priorities [4].

3. LIMITATIONS TO PATIENT ENGAGEMENT IN AHUS HTA

Despite this, significant systemic barriers exist to meaningful patient engagement in aHUS HTA.

3.1 Little and inconsistent engagement

In HTA, patients are often engaged at certain stages in the process that have periods of inclusion, such as public consultations, rather than throughout the HTA process. As a result, offered engagement opportunities may not represent the true experiences and priorities of the whole range of patients affected by aHUS because patient involvement lacks clarity and comprehension to depoliticize aHUS patient life experiences through tokenistic consultation which attempts peer to peer notion of aHUS fully understood. However, inconsistency in these processes is similarly identifiable across HTA bodies or jurisdictions [5].

3.2 Transparency

The absence of transparency in HTA processes regarding when patients are involved, how patients are identified,

selected, and included, creates uncertainty for patient groups, and causes them to question how their input is being considered in the decision-making process. This lack of transparency reduces trust in the process, making them less likely to engage [6].

3.3 Limitations on Resources

For rare diseases such as aHUS, patient advocacy organizations often do not have the funds, knowledge, or manpower are needed to meaningfully engage in HTA processes. As described in the interviews in section 2.4.4, these patient groups find it challenging to synthesize high-quality

evidence and to navigate the complex HTA environment [6].

3.4 Data Collection Issues

It is inherently challenging to capture all patient experiences in a format which is structured and measurable and that covers aspects such as symptoms, treatment burden, and QoL, in addition to how these interact with one another. For aHUS specifically, it can also be challenging to focus on producing values that include the psychological impacts, and societal impacts since focus tends to be more on clinical data [5].

Table 1: Challenges involved in aHUS

Challenge	Description	Impact
Little and Inconsistent Engagement	Patients are engaged only at specific stages (e.g., public consultations), not throughout the HTA process, leading to tokenistic involvement.	Fails to capture the full range of aHUS patient experiences, reducing the relevance of HTA decisions.
Lack of Transparency	Unclear processes for patient identification, selection, and inclusion in HTA create uncertainty.	Reduces patient trust and willingness to engage, undermining the credibility of HTA outcomes.
Limited Resources	aHUS patient advocacy groups lack funds, knowledge, and manpower to navigate complex HTA processes.	Hinders the ability to produce high-quality evidence, limiting patient influence on HTA.
Data Collection Issues	Difficulty in capturing structured, measurable patient experiences (e.g., symptoms, QoL, psychological impacts).	Focus on clinical data overlooks broader societal and psychological impacts, skewing HTA assessments.

4. WHY IT IS IMPORTANT TO INCLUDE PATIENT PERSPECTIVES IN AHTA

Including patient perspectives in aHTA is essential to the HTA decision reflecting the real burden of aHUS, as well as the value of

therapies. The following subsections will highlight keyways patients can contribute.

4.1 Capturing Lived Experience

Patients offer distinct perspectives on the day-to-day realities of living with aHUS, including symptom severity, frequency of relapses, side-effects of treatments, and psychological impacts. This qualitative

data bring a richer understanding to clinical trial outcomes to give a more rounded view of the disease experience [7].

4.2 Identifying Unmet Needs

Patient involvement can identify deficiencies in existing paradigms of treatments, diagnostic journeys, and other support that may not have come to light through clinical data. For example, patients may identify delays in their diagnosis, or relay difficulties in accessing specialized care, which can be important in HTA assessments [8].

4.3 Informing Patient-Reported Outcomes and Quality of Life

Patient-reported outcomes (PROs) and Quality of Life (QoL) measures provide a nuanced investigation into treatment success beyond traditional clinical endpoints. PROs can evaluate multiple areas of impact for patients living with aHUS: work, education, social life, and mental can't be overestimated in an HTA context [7].

4.4 Quantifying Broader Societal Impacts

Patient experiences allow us to quantify indirect costs of aHUS, including loss of productivity, impact on caregivers (potential for this?), need to change or modify their home environments. These elements are part of the economic assessments in HTA purposes, ensuring a full societal impact of aHUS is considered [8].

5. PROPOSED SOLUTIONS FOR ENHANCED PATIENT INVOLVEMENT

To address the challenges outlined above, a multi-faceted approach is required to create a patient-centric HTA framework for aHUS.

5.1 Increase Transparency and Accessibility

HTA organizations should publish clear guidance on patient involvement, covering timelines, required submission formats, and decision-making processes. Summarized versions of HTA reports can help patient groups be more accessible [9].

5.2 Support Patient Advocacy Groups

Funding and training initiatives can help aHUS patient groups gain strong evidence, train advocates, and engage in HTA. Working in partnerships with university departments or HTA agencies can also assist this process [9].

5.3 Ensure Diverse Representation

Actively seeking diverse patient representatives, in respect to age group and disease stage and geographical location, will increase insight and understanding of the aHUS population [9].

5.4 Comprehensive Patient Registries

Working with patient registries, such as the global aHUS registry, can provide data from the community on disease progression, treatment patterns, and PRO's. By creating access to patient-derived evidence, we build the evidence base for HTA [10].

5.5 Bridge Cultural and Language Gaps

Language can be difficult, and HTA terminology can be opaque. Providing resources to assist patient advocacy groups translate their own experience into language relevant to HTA processes ensures that their perspectives are considered in a meaningful way [10].

Table 2: Solutions for Enhanced Patient Involvement

Solution	Description	Expected Outcome
Increase Transparency and Accessibility	Publish clear guidance on patient involvement processes, including timelines and submission formats, and provide summarized HTA reports.	Builds trust and encourages patient participation by making HTA processes more accessible.
Support Patient Advocacy Groups	Provide funding and training to aHUS advocacy groups, fostering partnerships with universities or HTA agencies.	Enhances advocates' ability to produce high-quality evidence and engage effectively in HTA.
Ensure Diverse Representation	Actively seek patient representatives from varied age groups, disease stages, and geographical locations.	Provides a comprehensive understanding of the aHUS population, improving HTA relevance.
Comprehensive Patient Registries	Leverage registries like the global aHUS registry to collect data on disease progression, treatment patterns, and PROs.	Strengthens the evidence base for HTA with patient-derived real-world data.
Bridge Cultural and Language Gaps	Offer resources to translate patient experiences into HTA-relevant terminology.	Ensures meaningful inclusion of patient perspectives, overcoming communication barriers.

6. ORGAN-ON-CHIP TECHNOLOGY: A NEW FRONTIER FOR PATIENT INVOLVEMENT

New technologies, including organ-on-chip, provide a novel structure to enable patient perspectives on aHUS research and HTA.

6.1 Personalized Disease Modeling

Organ-on-chip technology takes induced pluripotent stem cells (iPSC) from patient aHUS samples and derives kidney-on-chip or vascular on-chip models based on individuals' specific genetic mutations and complement dysregulation. These models will return personalized insight into the functioning mechanisms of the disease.

6.2 Testing Treatment Efficacy and Toxicity

With patient-derived organ-on-chip models, potentially therapeutic therapies can be trialed within a patient context for their effectiveness and side effects, such as in the case of a complement inhibitor. This ultimately optimizes treatment decisions and minimizes adverse events.

6.3 Reducing Animal Testing

Organ-on-chip models help minimize usage of animal models for drug testing by providing a human-relevant system of pharmacological testing that meets ethical standards and promotes drug development.

6.4 Understanding Disease Heterogeneity

aHUS presents significant heterogeneity in clinical presentations and responses to treatments. Organ-on-chip models can help explain variability in patient response to

treatments, leading to more precise treatments.

6.5 Facilitating Patient Education and Engagement

Visual presentations of aHUS impact of patient derived “mini-organs” would help patients understand and engage in their care, leading to greater participation in HTA [11].

7. CASE STUDY: SARAH’S JOURNEY WITH AHUS

Sarah is a 32-year-old woman with aHUS and demonstrates the significance of incorporating patient perspectives into HTA. Sarah was misdiagnosed and continuously relapsed, leading to chronic exhaustion and inability to work and focus on taking care of her family. Sarah participated in an aHUS patient registry, and her data contributed to real-world evidence used in HTA evaluations, which emphasized the need for diagnosis sooner than later and access to complement inhibitors. Sarah’s case exemplifies the importance of utilizing the lived experience in order to inform HTA evaluations [12].

8. FUTURE DIRECTIONS AND CALL TO ACTION

Moving forward with patient-centric HTA in aHUS will require involvement from a variety of stakeholders, such as HTA bodies, patient advocates, researchers, and policymakers.

8.1 Empower patients advocacy

Training and resources for aHUS patient advocacy groups to enhance their capacity to engage in the HTA conversation, and develop high-quality evidence about aHUS, are worthwhile investments.

8.2 Enhance research

Funding research on patients reported outcomes (PROs), quality of life measures (QoL), or organ-on-a-chip models can

provide a wealth of high-quality patient-centered evidence to support HTA evaluations.

8.3 Develop collaborations

Collaborations between HTA bodies, patient organizations, and researchers can promote a more inclusive HTA environment, and allow aHUS patients’ perspectives to be represented and incorporated into decisions about funding [13].

9. CONCLUSION

Patient-centric HTA is key to ensuring that aHUS therapies are assessed in a way that resembles the true needs and lived experiences of those with any form of aHUS. Stakeholders can use systemic barriers, do the things we recommend, and apply models like organ-on-chip to create a more equitable and effective HTA process. We urge all stakeholders to work collaboratively to bridge the gap between recognizing the value to patients or patients’ value to taking concrete steps to improve aHUS patients’ outcomes.

10. REFERENCES

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