Management of Atypical Hemolytic Uremic Syndrome: Clinical Effectiveness and Guidelines
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Acknowledgments:

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada’s health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.
Research Questions

1. What is the clinical effectiveness of eculizumab for patients with native-kidney atypical Hemolytic Uremic Syndrome (aHUS) who undergo one year of treatment and experience a remission of their disease?

2. What is the clinical effectiveness of eculizumab for patients with recurrent aHUS in the renal allograft who undergo one year of treatment and experience a remission of their disease?

3. What is the clinical effectiveness of renal transplantation for patients with aHUS who progress to end stage renal disease?

4. What is the clinical effectiveness of renal transplantation for patients with aHUS who progress to end stage renal disease treated prophylactically with eculizumab?

5. What are the evidence-based guidelines on the management of aHUS?

Key Findings

One systematic review and six non-randomized studies were identified regarding the management of aHUS.

Methods

A limited literature search was conducted on key resources PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2013 and May 16, 2018. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.
Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
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<tr>
<td>Patients with atypical hemolytic uremic syndrome (aHUS)</td>
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<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>Q1-2: Eculizumab</td>
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<tr>
<td>Q3: Renal transplantation</td>
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<tr>
<td>Q4: Renal transplantation treated with Eculizumab prophylactically</td>
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<tr>
<td>Q5: Management of aHUS</td>
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<tr>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td>Q1-4: Any comparator, no comparator</td>
</tr>
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<td>Q5: No comparator</td>
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<tr>
<td><strong>Outcomes</strong></td>
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<tr>
<td>Q1-2: Risk of disease relapse, when do relapses occur, what are the risk factors for relapses (including genetic and functional complement abnormalities)</td>
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<tr>
<td>Q3-4: Risk of aHUS flare post-transplant, when do flares occur post-transplant, what are the risk factors for disease flare post-transplant?</td>
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<td>Q5: Guidelines regarding the management of aHUS</td>
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<tr>
<td><strong>Study Design</strong></td>
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<tr>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines</td>
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</table>

**Results**

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

One systematic review and six non-randomized studies were identified regarding the management of aHUS.

Additional references of potential interest are provided in the appendix.

**Overall Summary of Findings**

One systematic review, and six non-randomized studies were identified regarding the management of aHUS. Detailed study characteristics are provided in Table 2.

Conclusions from the identified studies indicate that eculizumab is a clinically effective treatment for patients with aHUS, including pregnancy-associated aHUS. The systematic review included three studies, where thrombotic microangiopathy (TMA) event-free status was achieved in 84% of patients in the prospective studies. Similar results were observed in one of the non-randomized studies, which reported TMA event-free status in 95% of patients after two-years of treatment with eculizumab. Eculizumab was shown to be clinically effective in both the treatment of aHUS upon disease onset as well as maintenance of aHUS remission. It was also shown to be clinically effective when used prophylactically for patients with aHUS undergoing renal transplantation; however, one study did note that treatment schedules should be individualized with prophylactic use to avoid relapse, particularly for patients with factor H mutation.
Table 2: Summary of Included Studies

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study Objectives, Relevant Characteristics</th>
<th>Population, Setting</th>
<th>Intervention, Comparator</th>
<th>Results, Author Conclusions</th>
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<tbody>
<tr>
<td>Rathbone 2013¹</td>
<td>To determine the efficacy and safety of eculizumab for patients with aHUS, compared with current treatment options</td>
<td>All patients diagnosed with aHUS N = NR</td>
<td>Eculizumab compared with current treatment options</td>
<td>Compared with baseline measures, TMA event-free status was achieved in 84% of patients in the prospective studies. Extension phase studies indicated sustained benefit of treatment up to 114 weeks. Eculizumab is clinically effective for the treatment of aHUS</td>
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<tr>
<td>Ardissino 2018²</td>
<td>To assess maintenance treatment with eculizumab with an increased interval between subsequent doses, for maintaining aHUS into remission</td>
<td>Patients with aHUS (13 children, 21 female, median age 25 years) at disease onset N = 21</td>
<td>Treatment with eculizumab “standard schedule” (not reported) at disease onset for median of 2.6 months (range 0.4 – 24.6) Interval between doses was extended based on complement function</td>
<td>No patients relapsed during a median observation period of 26.9 months (range 0.8 – 80.9). The frequency of eculizumab administration can be safely reduced with complement activity monitoring, keeping the disease in remission</td>
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<tr>
<td>Huerta 2018³</td>
<td>Analysis of clinical and prognostic data from cases of p-aHUS</td>
<td>22 cases of p-aHUS from the Spanish aHUS Registry N = 22</td>
<td>10 patients received eculizumab 17 patients received plasma treatment</td>
<td>A positive renal response was observed in 3 out of 17 cases receiving plasma treatment. All 10 patients receiving eculizumab experienced an “excellent renal response”. Acknowledging the small sample size, this data suggests the efficacy of eculizumab treatment is greater than that of plasma therapies, in patients with p-aHUS</td>
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<tr>
<td>Fakhouri 2017⁴</td>
<td>Retrospective analysis of clinical and biologic data</td>
<td>Dialysis-free patients with aHUS who discontinued</td>
<td>Eculizumab treatment followed by</td>
<td>21 patients carried complement gene</td>
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</table>

¹ Systematic Review, 2 uncontrolled prospective multinational, multicenter studies and one uncontrolled multinational, multicenter retrospective study were included. 
² Non-Randomized Studies
³ Analysis of clinical and prognostic data from cases of p-aHUS. 
⁴ Retrospective analysis of clinical and biologic data.
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<td>de Andrade 2017²⁵</td>
<td>To assess the efficacy and safety of eculizumab in kidney transplant patients with aHUS</td>
<td>Kidney transplant patients, either with previous diagnosis of aHUS or onset of aHUS after transplantation N = 7</td>
<td>Therapeutic or prophylactic eculizumab (5 therapeutic and two prophylactic patients)</td>
<td>Improved TMA within 48 hours of treatment initiation and no relapse during an average 21-month follow-up in therapeutic group; also one death due to Aspergillus infection. For the prophylactic group, there was one case of relapsed TMA after 4 months, the other patient showed no symptoms after 16 months of follow-up. Briefly, prophylactic and therapeutic use of eculizumab was safe and effective; however, it was suggested that treatment</td>
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<td>from aHUS patients</td>
<td>eculizumab between 2010 and 2014, identified through the French aHUS registry database N = 38 (9 children, 129 adults)</td>
<td>discontinuation of treatment Median duration of treatment was 17.5 months</td>
<td>variants; however this did not appear to affect renal recovery under eculizumab 12 (31%) of patients experienced aHUS relapse after a median follow-up of 22 months; this was not observed in patients without rare genetic variants detected. Reintroduction of eculizumab within 48 hours lead to hematologic remission in less than 7 days as well as return to baseline levels of serum creatine. Authors concluded that pathogenic variants in complement genes were associated with higher risk of aHUS relapse with discontinuation of eculizumab.</td>
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<td>Mallett 2015⁵</td>
<td>To report on the clinical characteristics and outcomes for patients with aHUS treated with eculizumab Retrospective cohort study</td>
<td>Australian patients with aHUS within a compassionate access programme Median age of 23.5 years (IQR = 24.83 years); 8 patients were female, and 3 had a family history of aHUS N = 10</td>
<td>Eculizumab (median duration of treatment = 911.5 days), for the following:  • acute aHUS (3 patients)  • relapsing and refractory acute aHUS (3 patients)  • de novo aHUS post-renal transplantation (2 patients)  • recurrent aHUS post-transplantation (1 patient)  • transplantation with history of aHUS (1 patient)</td>
<td>9 patients achieved remission of aHUS and have continued treatment with eculizumab 2 of the 4 patients requiring renal replacement therapy (RRT) ceased RRT since treatment with eculizumab One death due to uncontrollable gastrointestinal aHUS manifestations In summary, eculizumab was an effective therapy for the aHUS cohort in this study</td>
</tr>
<tr>
<td>Licht 2015⁷</td>
<td>2-year extension of a phase 2 study to evaluate eculizumab in patients with long duration of aHUS and chronic kidney disease</td>
<td>Patients with a long duration of aHUS and chronic kidney disease N = 20</td>
<td>Eculizumab Median exposure of 114 weeks</td>
<td>Outcomes were assessed at 26 weeks, 1 year, and 2 years 19 patients achieved TMA event-free status by year 2 Hematologic normalization criteria was met by 18 patients at each time point Mean change of eGFR was not significant at 2 years compared to any time point Overall, the authors concluded eculizumab was well tolerated and without any new safety</td>
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*Note: TMA = thrombotic microangiopathy; aHUS = atypical hemolytic uremic syndrome; eGFR = estimated glomerular filtration rate.*
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<tr>
<td>Rathbone J, Kaltenthaler E, Richards A, Tappenden P, Bessey A, Cantrell A.</td>
<td>A systematic review of eculizumab for atypical haemolytic uraemic syndrome (aHUS).</td>
<td></td>
<td></td>
<td>signals, and maintenance of clinical benefit was observed at 2 years</td>
</tr>
</tbody>
</table>

References Summarized

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-Analyses

PubMed: PM24189082

Randomized Controlled Trials
No literature identified.

Non-Randomized Studies

PubMed: PM29046944


PubMed: PM28911789


PubMed: PM27799617


PubMed: PM29136640

PubMed: PM26247170


PubMed: PM25651368

Evidence-Based Guidelines

No literature identified.
Appendix — Further Information

Previous CADTH Reports


Evidence-Based Assessment – Coverage Decisions


Non-Randomized Studies – Duration of Treatment Unclear or Less Than One Year


PubMed: PM25384530

**Case Studies and Case Series**


PubMed: PM28224376


PubMed: PM29695177


PubMed: PM28858176


PubMed: PM28821363


PubMed: PM28176479


PubMed: PM28176471


PubMed: PM28104134


PubMed: PM28176477
PubMed: PM29225802

PubMed: PM28458317

PubMed: PM28104125

PubMed: PM28101432

PubMed: PM27646857

PubMed: PM28101502

PubMed: PM25941307

PubMed: PM25318620

PubMed: PM25752761

PubMed: PM25634788


PubMed: PM24933457


PubMed: PM25593925


PubMed: PM24656451


PubMed: PM24839895


PubMed: PM24843059


PubMed: PM24828571


PubMed: PM24317637


PubMed: PM25149852


Unclear duration of treatment


*PubMed: PM25486517*


*PubMed: PM26986861*


*PubMed: PM25815183*


*PubMed: PM25345382*

Guidelines – Rigour of Methodology Unclear


*PubMed: PM27550478*


*PubMed: PM27422619*


*PubMed: PM29058539*


*PubMed: PM26456110*
Review Articles


   PubMed: PM25859752


   PubMed: PM27110144


   PubMed: PM26536427


   PubMed: PM24526222


   PubMed: PM25400666


   PubMed: PM24249647


   PubMed: PM23747093


   PubMed: PM23399570


   PubMed: PM23486421
PubMed: PM24076560

PubMed: PM23810412

Additional References

PubMed: PM29563942

PubMed: PM24387053