aHUS – what’s new?

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aHUS Canada Meeting
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An international consensus approach to the management of atypical hemolytic uremic syndrome in children

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Overview

• The complement system – activation and regulation

• The spectrum of complement-mediated disease

• aHUS – a complement-mediated disease

• Diagnosis of aHUS

• Treatment of aHUS
The spectrum of complement-mediated diseases
Etiology based classification of TMA

Loirat et al, Pediatr Nephrol 2015
### Benefit of complement-targeting treatment supports common pathogenetic role for complement

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
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<tr>
<td>Hemolytic uremic syndrome</td>
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<tr>
<td>- “typical” HUS / STEC HUS</td>
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<tr>
<td>- atypical HUS</td>
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<tr>
<td>TMA post solid organ transplantation</td>
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<tr>
<td>- de novo TMA</td>
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<tr>
<td>- TMA recurrence</td>
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<td>TMA associated with pregnancy</td>
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<tr>
<td>TMA post hematopoietic stem cell transplantation</td>
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<td>TMA associated with glomerulonephritis</td>
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<td>TMA associated with drugs</td>
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<td>TMA associated with metabolic disease</td>
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<tr>
<td>TMA associated with infections</td>
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<td>TMA associated with malignant hypertension</td>
</tr>
</tbody>
</table>

Riedl / Licht et al, Semin Thromb Hemost 2014
Primary complement dysregulation

- Endogenous defects – mutations / autoantibodies
- Conditions resulting in EC activation and secondary complement activation
  - Drugs
  - Malignant hypertension
  - Pregnancy
- Conditions activating complement
  - Immune complexes
  - Autoantibodies
  - Infections
- Conditions inhibiting complement regulators
  - Shiga toxin
The complement system – activation and regulation
The complement system

• 1889 – Hans Ernst August Buchner
  ... detects that a cell free system that can kill bacteria.

• 1896 – Julius Bordet
  ... detects a heat-insensitive component with specific anti-microbial function (i.e. antibodies) and a heat-sensitive component with unspecific anti-microbial function (i.e. complement).

• 1900 – Paul Ehrlich
  ... coins the term “complement” (i.e. something that complements the function of antibodies).

• 1930 – Jackie Stanley
  ... establishes our current understanding of the complement system and its role for innate and acquired immunity.
Regulation Activation
Self
Foreign
Injury
Candida albicans
Self
Foreign
Regulation
Activation
The complement system

Zipfel and Skerka, Nat Rev Immunol 2009
Complement alternative pathway: Regulation and dysregulation on the endothelium
aHUS – a complement-mediated disease
Mutation in SCR15:
- cDNA: T2770A (exchange)
- Protein: Y899Stop (premature stop codon)

Consequence:
- CFH protein truncated
- CFH protein stays intracellularly and is not secreted

Licht et al, Am J Kidney Dis 2005
CFH mutations

CFH autoantibodies – DEAP HUS

- Dragon-Durey et al, J Am Soc Nephrol 2005:
  - Normal CFH levels
  - Decreased CFH activity
  - No CFH mutations
  - CFH autoantibodies in 6% of aHUS patients

- Jozsi et al, Blood 2008:
  - CFH autoantibodies bind and inhibit CFH C-terminus

- Jozsi and Licht et al, Blood 2008:
  - CFH autoantibodies in 11% juvenile aHUS patients
  - Patients lack CFHR1/3 expression
  - New aHUS subgroup: **DEAP HUS** (deiciency of CFHR and CFH autoantibody positive)

- Abarrategui-Garrido et al, Blood 2009:
  - CFH antibodies associated with CFHR1 deficiency
aHUS-associated complement defects

- **Loss of function mutations**
  - Factor H (CFH)
  - Factor I (CFI)
  - Membrane cofactor protein (MCP/CD46)
  - Thrombomodulin (THBD/CD141)

- **Autoantibodies**
  - CFH (in combination with CFHR3/CFHR1 deletion: DEAP-HUS)

- **Gain of function mutations**
  - CFB
  - C3

- **Diacylglycerol kinase-ε (DGKE)**

- **Plasminogen (PLG)**

Functional consequences of DGKE mutations

**Endothelial cells:**
- PAF
- PAI-1
- vWF
- TF
- tPA
- VEGFR2

**Platelets:**
- Granule secretion
- TA₂

**Podocytes:**
- Slit diaphragm function
- Nephrin endocytosis
Complement mutation – disease manifestation

Age at disease manifestation and genotype – renal outcome

Long-term outcome

• Relapse:
  - 40% overall risk (43% in children; 35% in adults)
  - 57% of relapses in children and 82% in adults during the first year (!)
    (92% of relapses in children with MCP/CD46 mutations)
  - 25% of relapses in all patients after the first year

• ESRD / death:
  - 17% in children and 46% in adults at 1 month
  - 36% in children and 64% in adults at 5 years

• Extrarenal manifestation:
  - Overall 10-30%
  - Most prominent organ system – CNS (11%)
  - Other organ systems – GI (e.g. liver/pancreas), heart, etc.

Individual vs. combined complement mutations

- Patients carrying *any* mutation 44% (350/795)
- Patients carrying *single* gene mutation 40.6%
- Patients carrying *combined* mutations 3.4%
- Additional mutation risk \(\text{MCP/CD46}\) 22.6%
- Additional mutation risk \(\text{CFI}\) 27%
- Additional mutation risk \(\text{CFH, C3, CFB}\) 8-10%
- Additional mutations have no impact on overall outcome (except for MCP/CD46)
- MCP/CD46 alone 18.5% vs. MCP/CD46 combined 50% ESRD at 3 years
Risk haplotypes

- CFH-H3 tgtgt
- MCP ggaac
- C3 R139W + CFH-H3 tgtgt  4 fold risk
- C3 R139W + MCP ggaac  3 fold risk

Diagnosis of aHUS
Diagnostic work up for aHUS includes:
- Screening for mutations in target genes
- MLPA for CFHR1-5
- ELISA for CFH autoantibodies

Diagnostic algorithm for aHUS

Loirat et al, Pediatr Nephrol 2015
Genetic testing of aHUS patients

- First episode of aHUS: Start genetic screening after confirmation that there is no causative disease, no STEC infection, no severe ADAMTS 13 deficiency and no hyperhomocysteinemia/methyl-malonic aciduria.

- Start genetic screening without delay if:
  - Relapse of HUS
  - Familial history of non synchronous HUS
  - Pregnancy/post-partum-HUS
  - De novo post-transplant HUS

- Genetic screening required before kidney transplantation for aHUS. Not justified before transplantation for STEC-HUS, unless this diagnosis was uncertain/unproven.

Genetic characterization necessary for:
- Confirmation that the disease is complement-dependent or not
- Establishing prognosis, risk of relapses and of progression to ESRD
- Genetic counselling to parents and family
- Decisions for kidney transplantation: choice of the donor, treatment schedule to prevent or treat post-transplant recurrence, decision of combined kidney-liver transplantation
- Further prospective studies are required to establish the safety of complement blockade treatment discontinuation, according to the genetic background

Loirat et al, Pediatr Nephrol 2015
Treatment of aHUS
Plasma therapy

• First-line treatment (2009)

• Plasma infusion:
  - Replacing deficient and/or defective complement factors
  - Dose limited because of volume challenge

• Plasma exchange:
  - Removing mutant complement factors and/or antibodies
  - Restoring functional complement regulators
  - Providing larger amounts of plasma than with infusion

Ariceta et al, Pediatr Nephrol 2009
Diagnosis of HUS
Atypical presentation (see step one)

Plasmapheresis within 24 hours of diagnosis
Exchange 1.5 x plasma volume (60-75ml/kg) per session
Replace with fresh frozen plasma or Octaplas®

Repeat plasmapheresis daily x 5
Then 5 sessions per week for 2 weeks
Then 3 sessions per week for 2 weeks

Assess outcome at day 33
Go to step 4

Exceptions

Withdrawal
Alternative diagnosis
Complication of plasmapheresis
Early remission

Ariceta et al, Pediatr Nephrol 2009
Limitations and complications

• Not all aHUS patients respond to plasma therapy.

• Patients with mutations of membrane-anchored complement regulators (e.g. MCP/CD46; THBD/CD141) may not benefit from plasma therapy. (Beresin et al, J Am Soc Nephrol 2013)

• Possibility for multiple mutations (e.g. in MCP/CD46 mutation carriers). (Beresin et al, J Am Soc Nephrol 2013)

• Secondary failure to plasma therapy in patient with CFH mutation. (Nathanson et al, Pediatr Nephrol 2006)

aHUS outcome

- Sudden death and vital organ damage.\(^1,2\)
- 33-40% of patients die or progress to ESRD with the 1st clinical manifestation.\(^1,3\)
- Chronic progressive course with premature mortality.\(^1,3,4\)
- 65% of all patients die, require dialysis or have permanent renal damage within the 1st year after diagnosis despite plasma exchange or plasma infusion.\(^1\)

aHUS outcome

![Graph showing overall renal survival without ESRD (%)](image)

- Pediatric onset
- Adult onset

*P < 0.001*

<table>
<thead>
<tr>
<th>Years</th>
<th>Pediatric onset</th>
<th>Adult onset</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>89</td>
<td>125</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>0</td>
</tr>
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Number of aHUS patients at risk

aHUS outcome

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Eculizumab (Soliris®)

- Humanized monoclonal anti-C5 antibody

- Leaves proximal complement intact

- Weak anaphylatoxin (C3a)

- Immune complex clearance (C3b)

- Microbial opsonization (C3b)

- Blocks terminal complement

- Binds with high affinity to C5

- Blocks activation of C5 to generate C5a and C5b

- Blocks activation of terminal complement (C5b9)

**aHUS treatment**

Rother et al, Nat Biotechnol 2007
First successful use of eculizumab in aHUS

Eculizumab

Diagnosis

Plasmapheresis

Platelets

Creatinine

Platelet Count (per mm$^3$)

Creatinine (mg/dl)

Haptoglobin (g/liter)

Time (days)

First successful use of eculizumab in aHUS
Eculizumab is superior to plasma therapy in controlling complement.

Heinen et al, Mol Immunol 2012
Meningococcal infection prophylaxis

**Meningococcal vaccination**

- Vaccination is mandatory, before eculizumab initiation or as soon as possible if urgent eculizumab therapy is indicated.
- **Quadrivalent conjugate vaccines** (anti-A, C, Y, W) (Menactra™ (USA) (age > 9 months), Menevo® (age ≥ 2 years) or Nimenrix® (age ≥ 1 year)).
- Recent studies showed that Menevo® was well tolerated and highly immunogenic in healthy infants aged 2 to 12 months (103,104).
- **+ Anti-B vaccine** (Bexsero® (age ≥ 2 months), where available.

**Efficacy of anti-meningococcal (vaccine) antibodies** is uncertain in patients with complement deficiency, complement blockade or immnosuppressive therapy. We therefore recommend additional antibiotic prophylaxis, allowing prompt initiation of eculizumab.

Patients with ESRD due to aHUS should be vaccinated prior to registration on the waiting list (105,106). Also consider vaccination of household close contacts (at least siblings and parents).

**Which antibiotics?**

- Methylpenicillin (twice daily, full dose adapted to weight). Despite the reduced sensitivity of approximately 20% of meningococci towards penicillin, methylpenicillin retains its overall efficacy to prevent meningococcal infection.
- Macrolides in case of allergy to penicillin (however macrolides interfere with calcineurin inhibitors metabolism in transplanted patients)
- Avoid rifampicin or fluoroquinolone for long term prophylaxis, to limit the risk of inducing bacterial resistance (except in case of contact with a patient with invasive meningococcal infection)
- Other antibiotics may be recommended by local experts.

**Which duration?**

- Obligatory during 2 weeks after vaccination in patients receiving eculizumab
- Obligatory in some countries (France, UK) as long as the patient receives eculizumab (+ 60 days after eculizumab discontinuation)
- Discrepant current practice in other countries
- Continuous antiibioprophylaxis is recommended by the majority of authors of this review

**Information card**

- Education on signs of meningococcal infection to ensure early recognition and treatment
- Consider prescription of ceftriaxone for immediate access at home in remote areas
- Travel/holidays should be carefully prepared (information on meningococcal epidemiology in the visited country, prior written contact with local teams, information to the patient of where to go, which doctor/department/phone numbers…)
- An **Information card** to be carried by the patient or his/her care giver, to be shown to medical staff in case of symptoms suggesting infection
Treatment of patients with antibody-mediated aHUS

First episode of aHUS

- Eculizumab (or PE if eculizumab not available) within 24-48 hours after onset

Positive for anti-CFH antibodies

No or mild extra-renal manifestations

Continue eculizumab
Consider adding corticosteroids and/or MMF in attempt to reduce antibody titer
Efficiency / benefits to be established

Stop PE / eculizumab when anti-CFH antibody titer < 1000 AU/ml

Maintenance treatment with MMF + corticosteroids, guided by anti-CFH antibody titer

Consider treatment withdrawal after ≥ 1 year in patients with stabilized remission of HUS, anti-CFH antibody titer < 1000 AU/ml and normal C3

Severe extra-renal manifestations

Switch to PE or continue PE + cyclophosphamide pulses (x2-5) or rituximab + corticosteroids

Consider combining PE with eculizumab + cyclophosphamide pulses or rituximab + corticosteroids

Further studies are required to document which option is the best for which patient

Loirat et al, Pediatr Nephrol 2015
Treatment duration in aHUS

- In the pre-complement blockade period, the risk of relapse after the first year in patients alive without ESRD at 1 year follow-up, was 20-30% in patients with CFH/CFI mutations or no complement mutation identified, while it was 92% in children with MCP mutation. Despite a relapsing course, children with MCP mutation retained a relatively favourable prognosis (17% ESRD at 5 years follow-up) (3).
- Nobody knows what will be the relapse rate after complement blockade discontinuation in patients who survived and have preserved renal function under complement blockade.
- Strict monitoring (twice weekly urine dipstick) for early detection of relapse and immediate re-initiation of complement-blockade treatment in case of relapse can limit the risk of poor outcome and renal sequel (142).

- The frequency of cardio/cerebro vascular complications and of arterial stenosis in aHUS patients compared to patients with CKD due to other causes is not documented. Therefore this problem currently is not demonstrated as a reason for life-long complement blockade.

- Neither vaccination nor anti-influenza guarantee protection against meningococcal infection in patients receiving terminal complement blockade therapy.

- Long term IV infusions may lead to vascular access obstacles.
- Twice monthly IV treatment—particularly if performed in hospital—may be unacceptable as a life-long social commitment.
- Access to eculizumab both logistically and financially may be limited in some settings.
Management of aHUS patients with kidney transplants

Loirat et al, Pediatr Nephrol 2015