HUS – Current approaches

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HUS: the most common thrombotic microangiopathy in children

1. Basement membrane of the glomerular capillary
2. Endothelial cell
3. Subendothelial edema
4a. Toxins and toxic compounds
   Complement abnormalities
4b. Thrombocytopenia
   AKI
   Hemolytic anemia
   Schizocytes

HUS: the most common thrombotic microangiopathy in children
In real life...

Subendothelial edema

Schizocytes
Acute onset: asthenia, pallor, oliguria
Sometime seizures

- Hemolytic anemia
- Thrombocytopenia
- Acute renal failure

Extrarenal involvement (CNS, heart, pancreas)
Typical/atypical HUS

- **90% Typical HUS (D+)**
  - Infants and young children (62% < 3 yrs)
  - Prodromic diarrhea (bloody stools)
  - Infection with *E. coli* secreting toxins (STEC)
  - Good prognosis in most patients

- **10% Atypical HUS (D-)**
  - No prodromic sign
  - Heterogenous group of diseases
    - Complement abnormalities (inherited, immunization)
    - Systemic disease: SLE, cancer, allograft nephropathy
    - Toxic exposure: anticalcineurins, radiotherapy
  - Poor prognosis (extrarenal damage)
Thrombotic microangiopathy: a wide spectrum

- Congenital ADAMTS13 deficiency
- Anti-ADAMTS13 antibodies
- Thrombotic thrombocytopenic purpura
  - ADAMTS13 activity <10%
- HELLP syndrome
- Hemolytic uremic syndrome

HUS with coexisting disease / condition
- Bone marrow transplantation
- Solid organ transplantation
- Malignancy / cancer chemotherapy
- Autoimmune disorders (SLE, antiphospholipid syndrome, scleroderma, dermatomyositis)
- Drugs (calcineurin inhibitors, sirolimus and anti-VEGF agents)
- Malignant hypertension
- HIV infection

Streptococcus pneumoniae – HUS
- Influenza A / H1N1-HUS

- STEC-HUS
- Cobalamin C defect-HUS
- DGKE mutation-HUS
- Alternative complement pathway dysregulation-HUS
- Mutations in CFH, CFI, MCP, C3, CFB, THBD
- Anti-CFH antibodies

Hereditary

Autoimmune

Infectious
D+ HUS

Origins of the E. coli Strain Causing an Outbreak of Hemolytic-Uremic Syndrome in Germany
Progression of E coli O157:H7 infection in children
Adhesion of *E. coli* to enterocytes

Production of shigatoxines

Typical HUS: consequences of STEC infection

\(\text{Shiga-like toxin Escherichia coli or verotoxin}\)
Ingestion of STEC

- Contaminated food/water
- Contact with ruminant animals
- Contact with an infected person

Diarrhea 95%

Bloody diarrhea 60%

HUS 5-15%

Dialysis required ~60%

Transfusion required ~80%

Complications
- Neurological ~20%
- Intestinal/pancreatic ~10%
- Cardiac 2-5%

Death 1-4%

Full recovery 70%

Sequelae 30%

5 yr follow-up

Pallor, fatigue, petechiae/bruising
reduced urine output, edema

Thrombocytopenia + Microangiopathic anemia
(schizocytosis, increased LDH, decreased haptoglobin)
- Acute renal failure

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STEC-HUS: an unalterable scenario in children
Online epidemiological survey in children < 15 yrs

- ~100 cases per year
- Annual incidence
  - 0.7 per 100,000 children < 15 yrs
- Comparable
  - To others occidental Europe countries
  - To USA and Canada
- High incidence in Argentina
  - 22 per 100,000 children < 5 yrs

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Epidemiology of D+ HUS

- Mainly isolated cases
- But some outbreaks

- "At-risk" geographical zones
- "At-risk" seasons
- "At-risk" age groups
At-risk geographical areas
At-risk groups

At-risk age groups: < 3 ans

At-risk season: end of summer time

Tahden, PLoSONE 2016
Typical HUS, as a consequence of STEC infection

(Shiga-like toxin Escherichia coli or verotoxin)

- **Contamination**
  - Food
  - Inter-human contacts
  - Infected ruminants

- **Diagnosis**
  - Antibodies against STEC
  - Identification of STEC strains
  - Gene PCR encoding shigatoxins in stools (stx2)
Management

- Isolated/sporadic cases: adequate treatment of index case

- Pooled cases
  - Risk of outbreak
  - Epidemiological investigation (Public Health Agency)
  - Human and veterinary microbiological investigation
Risk factors within the previous 2 weeks

- Unpasteurized milk
- Raw cheese
- Un-/poorly-cooked meat (ground beef)
- Salami
- Raw vegetables, lettuce, radish sprouts
- Fruits with skin, unpasteurized apple cider/juice
- Ingestion of water from lakes, rivers, pool, etc.
- Contacts with farm animals
- Special events (party, marriage, travel)
Treatment: supportive measures

- ± Dialysis (temporary)
- ± Antibiotics (azithromycin)
- ± Blood transfusion
- ± Anti-hypertensive therapy
- ± High-dose frusemide/bumetamide if diuresis
- ± Feeding adapted to digestive conditions

In case of lifethreatening complication:
- Plasmapheresis ?
- Eculizumab (Soliris®) – 3 doses suggested

Avoid
- Platelet transfusion
- Corticosteroids, heparin, aspirin, dipyridamole,
Treatment: supportive measures

- 36% Dialysis (PD) + blood transfusion
- 47% Blood transfusion without dialysis
- 2% Dialysis without blood transfusion
- 16% Neither dialysis nor blood transfusion

Median duration for hospital stay: 10 days [2 – 48]
Outcomes

- Death (neurological/cardiac) 1-4 %

- Long-term renal sequellae 30-40 %!
  - Proteinuria – HTN – CKD
  - ESRD: 5 to 10 % (no recurrence after kidney Tx)
  - At least 1 work-up per year
  - Recommend normal-low sodium/protein diet, avoid overweight
  - In some cases, start ACEi/ARB

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Prognostic factors

- Dialysis required for > 10 days
- Neurological involvement
- Leukocytosis
- Inherited predisposition factors?
Antibiotic prophylaxis in sibs (azithromycin)

Antibiotic treatment of any *E coli* O157 infection

Avoid treatment of diarrhoea with antimotility agents

Immunisation anti-shiga-like toxins?
Conclusions

- Think of HUS!
- Mainly in children < 5 yrs of age
- Prevention ++
- Online epidemiological survey
- Early treatment in specialized unit
- Long-term follow-up
Dual role of complement

**Defense against infection**
- C3bBb
- Amplification loop
- C5b-9
  - Membrane attack complex (MAC)
  - Terminal complement complex (TCC)
- Opsonisation
- Phagocytosis
- Chemotactic factors
- Clearance of microbes

**Protection of host cell membranes**
- C3b
- Self
  - Negatively charged cell surface polyanions (heparin, sialic acid, GAGs)
- Membrane attack complex (MAC)
- Terminal complement complex (TCC)

**Complement regulatory proteins**

**Preservation of cell surface from C3b deposits and complement activation**

Courtesy Dr V Fremeaux-Bacchi
In 30 to 40% of patients, no complement abnormality could be identified, including DGKE mutations

Age at onset of atypical HUS
Genetic abnormalities and clinical outcomes in aHUS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein Affected</th>
<th>Main Effect</th>
<th>Frequency</th>
<th>Response to Short-Term Plasma Therapy</th>
<th>Long-Term Outcome</th>
<th>Outcome of Kidney Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>Factor H</td>
<td>No binding to endothelium</td>
<td>20–30</td>
<td>Rate of remission: 60% (dose and timing dependent)</td>
<td>Rate of death or ESRD: 70–80%</td>
<td>Rate of recurrence: 80–90%</td>
</tr>
<tr>
<td>CFHR1/3</td>
<td>Factor HR1, R3</td>
<td>Anti–factor H antibodies</td>
<td>6</td>
<td>Rate of remission: 70–80% (plasma exchange combined with immunosuppression)</td>
<td>Rate of ESRD: 30–40%</td>
<td>Rate of recurrence: 20%</td>
</tr>
<tr>
<td>MCP</td>
<td>Membrane cofactor protein</td>
<td>No surface expression</td>
<td>10–15</td>
<td>No definitive indication for therapy</td>
<td>Rate of death or ESRD: &lt;20%</td>
<td>Rate of recurrence: 15–20%</td>
</tr>
<tr>
<td>CFI</td>
<td>Factor I</td>
<td>Low level or low cofactor activity</td>
<td>4–10</td>
<td>Rate of remission: 30–40%</td>
<td>Rate of death or ESRD: 60–70%</td>
<td>Rate of recurrence: 70–80%</td>
</tr>
<tr>
<td>CFB</td>
<td>Factor B</td>
<td>C3 convertase stabilization</td>
<td>1–2</td>
<td>Rate of remission: 30%</td>
<td>Rate of death or ESRD: 70%</td>
<td>Recurrence in one case</td>
</tr>
<tr>
<td>C3</td>
<td>Complement C3</td>
<td>Resistance to C3b inactivation</td>
<td>5–10</td>
<td>Rate of remission: 40–50%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Rate of recurrence: 40–50%</td>
</tr>
<tr>
<td>THBD</td>
<td>Thrombomodulin</td>
<td>Reduced C3b inactivation</td>
<td>5</td>
<td>Rate of remission: 60%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Recurrence in one case</td>
</tr>
</tbody>
</table>

*Noris N Engl J Med 2009*
Eculizumab blocks terminal complement pathway

- Eculizumab binds with high affinity to C5
- Terminal complement activity is blocked
- Proximal functions of complement remain intact
  - Weak anaphylatoxin
  - Immune complex and apoptotic body clearance
- Microbial opsonization
Efficacy of eculizumab in aHUS: Case report
Efficacy of eculizumab in aHUS: Case series

Evolution of GFR change from baseline

Evolution of platelet count

Trial 1
- Clinical diagnosis of aHUS with:
  - Progressing TMA\(^a\)
  - ≥4 PE/Pt sessions in the week before screening
- 17 Patients were screened
- 17 Were treated with eculizumab

Trial 2
- Clinical diagnosis of aHUS with:
  - No platelet count decrease ≥25% during the 8-week observation period
  - ≥1 PE/Pt session every 2 weeks, but ≤3 times per week for ≥8 weeks
- 23 Patients were screened
- 20 Were treated with eculizumab
- 2 Were ineligible: 1 withdrew consent
Proposed treatment algorithm for anti-CFH antibody-associated HUS

Loirat Pediatr Nephrol 2016

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

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

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

Further studies are required to document which option is the best for which patient
Eculizumab offers to children with aHUS the best chance of sustained remission and full rescue of renal function.

The best way to monitor eculizumab treatment in the clinical practice has yet to be established (CH50 level?)

Prospective trials are required to establish if eculizumab withdrawal is safe, in which patients according to genetic background, and when.

### Table 4  Recommended eculizumab dosing regimen for patients with atypical HUS (aHUS)

<table>
<thead>
<tr>
<th>Patient body weight</th>
<th>Induction regimen</th>
<th>Maintenance regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 kg and over</td>
<td>900 mg weekly x 4 doses</td>
<td>1,200 mg at week 5; then 1,200 mg every 2 weeks</td>
</tr>
<tr>
<td>30 kg to less than 40 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3; then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>20 kg to less than 30 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>600 mg at week 3; then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10 kg to less than 20 kg</td>
<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5 kg to less than 10 kg</td>
<td>300 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 3 weeks</td>
</tr>
</tbody>
</table>
### aHUS - Transplantation

**aHUS carries a >50% risk of ESRD**

* aHUS is responsible for 2% to 5% of ESRD in children
* Overall recurrence rate: 50-80%
* Median time to recurrence: 30 days [0 day – 16 yrs]

<table>
<thead>
<tr>
<th>Biological defect</th>
<th>% of aHUS</th>
<th>% disease recurrence</th>
<th>% graft loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAMTS-13 deficiency</td>
<td>&lt;5</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Methylmalonic aciduria</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>DGKE mutation</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anti-factor H antibodies</td>
<td>5-10</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Factor H mutation</td>
<td>20-30</td>
<td>50-100</td>
<td>75-95</td>
</tr>
<tr>
<td>MCP/CD46 mutation</td>
<td>10-15</td>
<td>&lt;20</td>
<td></td>
</tr>
<tr>
<td>Factor I mutation</td>
<td>10-15</td>
<td>80-90</td>
<td>100</td>
</tr>
<tr>
<td>Factor B mutation</td>
<td>&lt;5</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>C3 mutation</td>
<td>5-10</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>THBD (thrombomodulin) mutation</td>
<td>&lt;5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No gene mutation</td>
<td>30-40</td>
<td>60</td>
<td>85</td>
</tr>
</tbody>
</table>
Death-censored graft survival after renal Tx

Graphs showing death-censored graft survival over time for different conditions.

No Recurrence

Recurrence

Mutation

No Mutation

Number at risk:
- No Recurrence: 27, 25, 21, 20, 15, 9, 3, 1, 0
- Recurrence: 44, 28, 20, 16, 9, 6, 4, 0, 0

Number at risk:
- Mutation: 48, 21, 16, 15, 13, 9, 5, 3, 2
- No Mutation: 23, 18, 16, 13, 7, 4, 3, 3

Le Quintrec Am J Transplant 2013
Use of Eculizumab post-Tx

- Anti-meningococcal immunization
- 375 mg/m² - Initially 1x week, then 1x 2 weeks
- To be continued lifelong?
- Individualized management according to
  - CH50 levels
  - Free eculizumab levels?
In summary...

First episode of TMA

- **Identify STEC-HUS**: Stool culture for STEC and PCR for six genes or test for free six or O157 antigen with or without LPS serology vs STEC serogroups
- **Identify SP-HUS**: Blood, CSF, pleural fluid culture, and test for SP soluble antigen with or without SP PCR, Chest radiograph or CT scan, DAT (direct Coombs test) with or without T-F antigen detection
- **Identify cblC-defect-HUS**: Plasma homocysteine concentrations; concentrations of methylmalonic acid in urine or plasma with or without MMACHC direct sequencing (if high concentrations of MMA)

**Supportive treatment**
- STEC-HUS
- SP-HUS
- cblC-defect-HUS

**Identify DGKE-HUS**
- DGKE sequencing

**Early onset (<2 years)**

**Initial work-up (<24–48 h)**
- **Supportive treatment**
  - Uncertain benefit from PE and eculizumab
- **Identify DGKE-HUS**
- **Early onset (<2 years)**

**Atypical HUS**

**During initial work-up (5–7 days)**
- Start daily PE with FFP (1–1.5 plasma volume per session)

**At any age**
- Personal or familial history of atypical HUS
- Recurrence of HUS in the renal graft

**Anti-CFH antibody >1000 U/mL**
- PE and IS with or without eculizumab

**First-line eculizumab within <24h of onset whenever possible. If not available, start PE with FFP (60 mL/kg per session; use PI if PE not available)**

**Switch to eculizumab**
- Haematological remission under PE does not invariably lead to renal function improvement

**Plasma C3, C4, CFH, and CFI with or without CFB dosages, anti-CFH antibodies, MCP expression on leukocytes**
- Screening for mutations in CFH, CFI, MCP, C3, CFB, THBD* and for CFH hybrid gene†

All patients with atypical HUS are eligible for eculizumab treatment, including those with normal platelet count. Do not wait for complement genetic tests to start eculizumab because the earlier the initiation of eculizumab, the better is the renal outcome.

**No trend towards increase in platelet count**
- Check complement blockade, eculizumab concentration, or CS polymorphism
- Recheck and complete differential diagnosis
- Non-complement-mediated TMA

**Persistent thrombocytopenia during first 7–10 days of eculizumab**
- Trend towards increase in platelet count
  - Check complement blockade
  - (CH50 <10%, eculizumab trough concentration >100 μg/mL)
  - Do not resume PE

**Persistent thrombocytopenia after 7–10 days of eculizumab**

**In summary...**
Thank you for your attention!