Updates in Atypical Hemolytic Uremic Syndrome

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Case presentation

19 mo ♂ presented with fever,lethargy, generalized edema and anuria following few days of mild GE.

PE: Temp: 39.5^{o}c BP:100/65 mmHg ,HR:125 ,

RR:60 with ill looking and edema .

Hb8gm/dl, platelet 50000,LDH12000,6%FRBC and schistocyte

BUN80mg/dl,Cr4.5mg/dl. No U/O.

Transferred toPICU and temporary PD catheter

inserted and FFP infusion started for him.

the 1st fluid revealed peritonitis350WBC 80%seg.

Blood culture was also +citrobacter.

Meropenem continued+IP antibiotics.

HUS profile:complement factor H, C3,FB, CD46 was nl.

Slightly low FI 34(38-58)mg/l,Nl ADAMTS 13

cont…

Case presentation

PD catheter changed to CAPD catheter after 4days.

With improvement of respiration, extubated and transferred to ward UO ↑gradually, but he became irritable due to very high BP220/150 and again transferred to PICU.

Meanwhile he developed fungal peritonitis, CAPD catheter D/C with acceptable U/O, but still high SCr 4mg/dl, systemic antifungal Rx continued.

Kidney biopsy 1.5 month after onset:

total sclerosis of 7/19 glomeruli , mesangiolysis in the remaining glomeruli, subendothelial widening and endothelial swelling and focal fibrin thrombi formation compatible with clinical diagnosis of HUS

Cont…

Case presentation

He was vaccinated against meningococci and 1wk later **Eculizumab** started for him

+ penicillin V

Now after about 8wks SCr is 1.9mg/dl with stable Hb and LDH

How long to continue the Eculizumab?

Cr ↓is due to Eculizumab Rx?

HUS

Introduction

HUS is characterized by MAHA, ↓platelet and AKI

HUS is caused by platelet thrombi in the microcirculation of the kidney and other organs

aHUS: genetic forms accounts for 60% of cases

aHUS :onset ranges from the neonatal to adulthood

aHUS :relapse after complete recovery is frequent

aHUS :60% of genetic forms progresses to ESRD

aHUS :associated genes include *C3*, *CD46* (*MCP*), *CFB*, *CFH*, *CFHR1,3,4 ,CFI,DGKE*, and *THBD*

Eculizumab and plasma manipulation are Rx options

Noris M, Bresin E, Mele C, et al. Genetic Atypical Hemolytic-Uremic Syndrome. 2007 Nov 16 [Updated 2016 Jun 9]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. **BookshelfURL:**https://www.ncbi.nlm.nih.gov/books

Epidemiology of aHUS

7/1000000 children in Europe

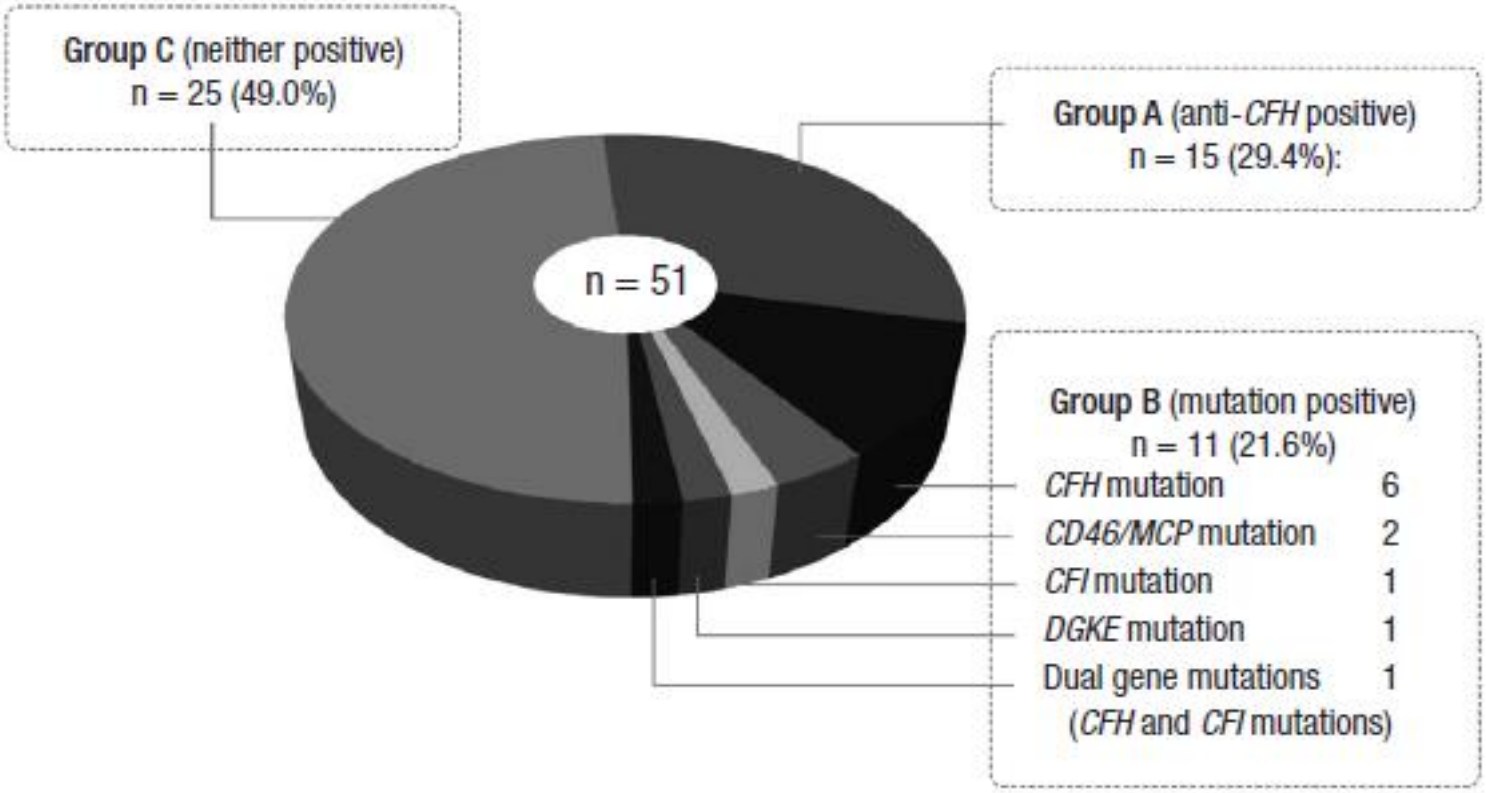
Mutations in the following genes account for 60% of aHUS
Complement factor H (*CFH)* 20 to 30%
*CD46,*previously known as (MCP) 5 to 15%
Complement factor I (*CFI*) 4 to 10 %
Complement factor 3 (*C3)* 2 to 10 %
Complement factor B (*CFB)* 1 to 4%
Thrombomodulin gene (*THBD),* 3 to 5%

- **VTN a new gene**

A significant number with more than one mutation
Low penetrance of the gene(<than ½)

Pediatr Nephrol. 2012;27(8):1283
Landau D,et al. J Pediatr 2001;138:412–7
Bu F,et al. Clin Dev Immunol 2012;2012:370426

aHUS in a Korean pediatric cohort



Cheong HI, et al J Korean Med Sci 2016; 31: 1516-1528

aHUS French cohort

90 children<16yrs,82pedigree,46♂
Sporadic68,familial22

CFH	**17(19%)**
MCP	13(14%)
CFI	8 (9%)
C3	6(7%)
CFB	1(1%)
Combined mut.	7(8%)
Anti-CFH Ab	10(11%)

Pathogenesis of aHUS

Dysregulation of the complement system

HUS results from a loss-of-function mutation in a regulatory gene (*CFH*, *CFI*, or *CD46*) or

Gain-of-function mutation in an effector gene (*CFB* or *C3*)

Autoantibodies against CFH 6-10%

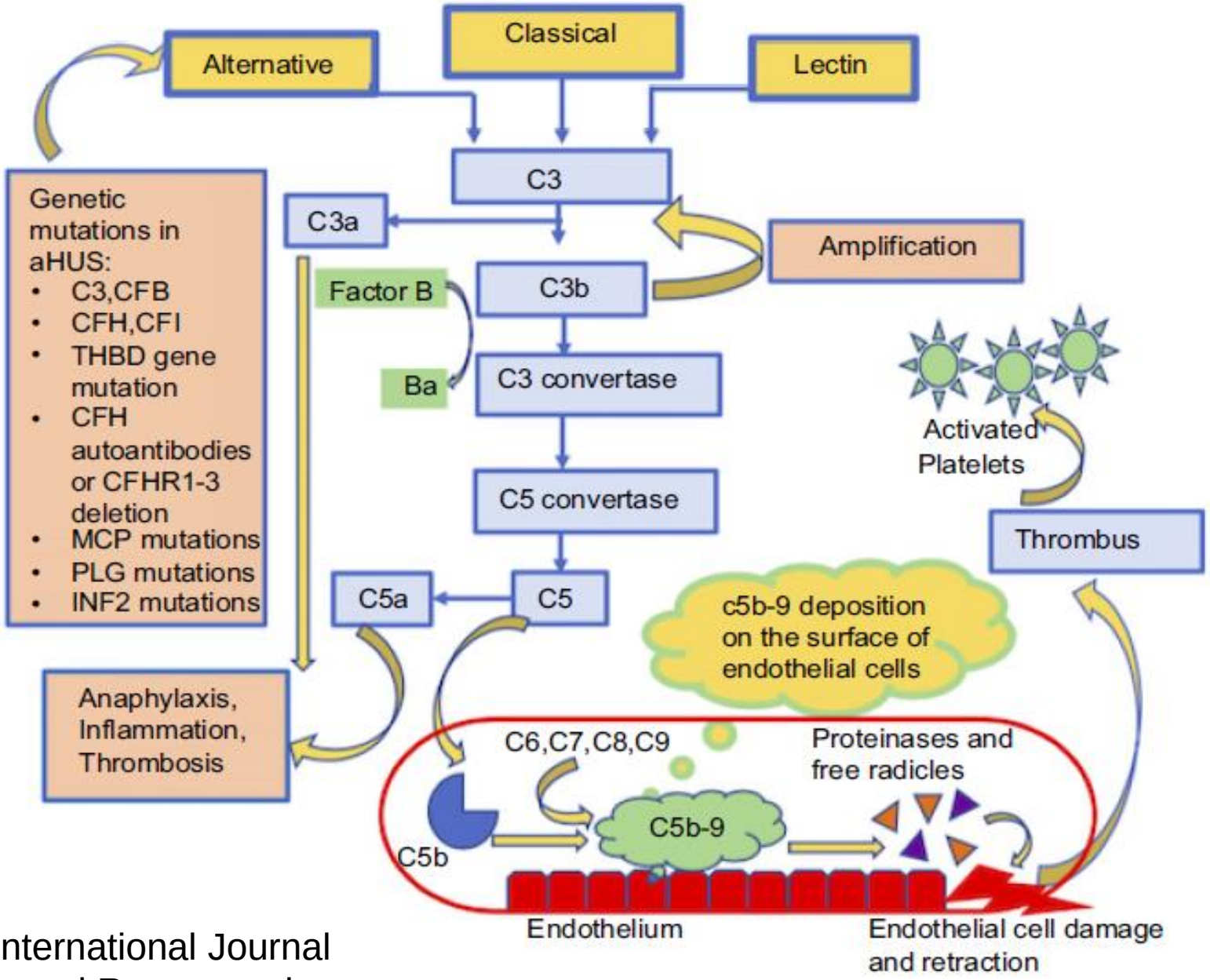
Complement-independent forms of aHUS, such as mutations in (DGKE*) and plasminogen (PLG)

Cobalamin C

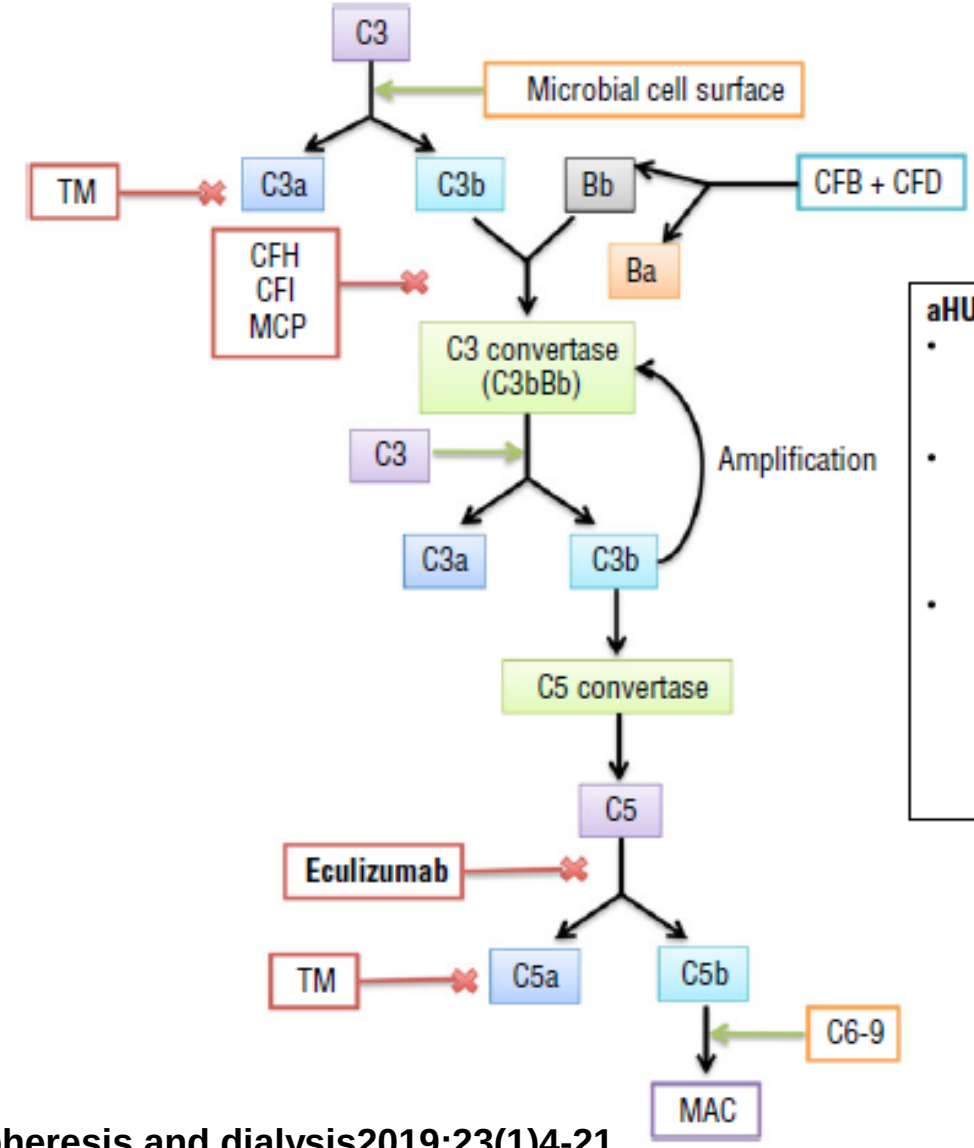
*Lemaire M,et al. Nat Genet 2013; 45: 531-6

Noris M,et al. Clin J Am Soc Nephrol 2010;5:1844–59

Fakhouri F, et al. Lancet 2017;38:817–24.



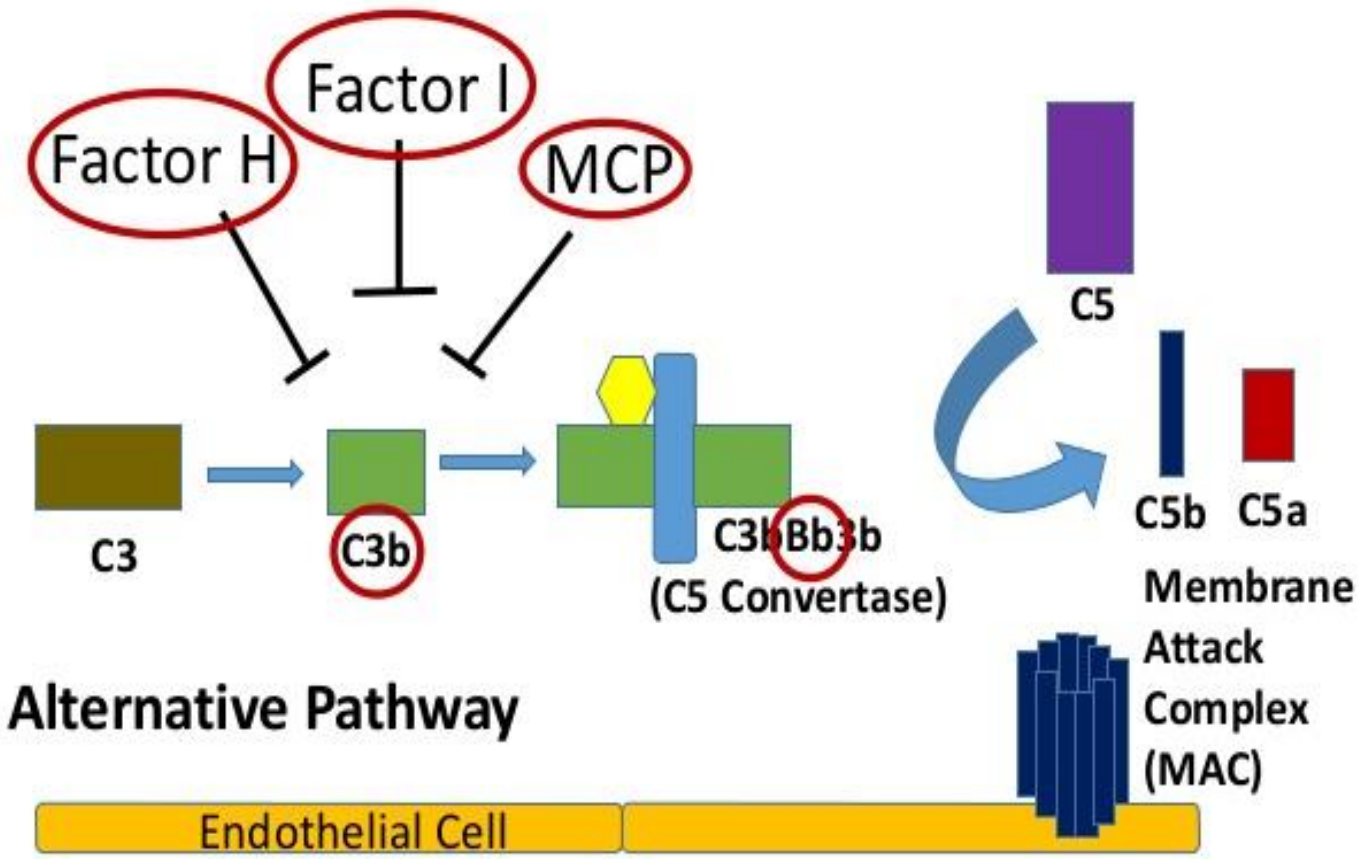
Raina r,et al.International Journal of Nephrology and Renovascular Disease2019:12 183–204.



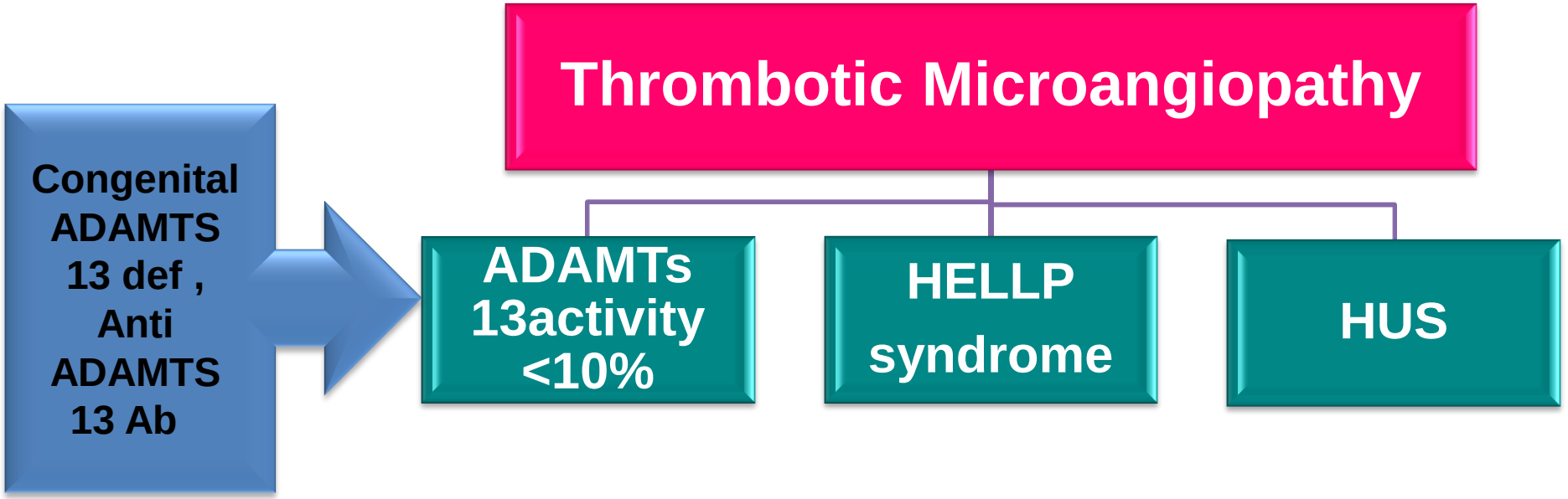
aHUS occurs via:

- Over-activation
  - Genetic mutations in C3, CFB
- Failed regulation
  - CFH autoantibodies
  - Genetic mutations in CFH, CFI, MCP, TM
- Triggers
  - Pregnancy
  - Transplant
  - Cancer
  - Viral infection
  - Pharmacologic agents

Therapeutic Apheresis and dialysis2019;23(1)4-21


Factor I
Factor H
MCP
C5
C5b
C5a
C3
C3b
C3bBb3b
(C5 Convertase)
Membrane
Attack
Complex
(MAC)
Alternative Pathway
Endothelial Cell

Thrombotic Microangiopathy



An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Chantal Loirat,et al. Pediatr Nephrol (2016)31:15–39

Diagnosis of aHUS

Rule out:1- coexisting conditions

2-S.pneumonia infection HUS

3-H1N1 infection

4-TTP

5-STEC-HUS

6-Cobalamin C defect-HUS

aHUS is likely

Clinical Characteristics of aHUS

aHUS onset from neonatal age to adulthood

- Poor outcome
- Frequent relapses
- 60% progress to ESRD
- Mutation of *C3*, *CD46*, *CFB*, *CFH*, *CFI*, and *THBD* predisposing factors rather than a direct cause

Ruggenenti et al 2001
Taylor et al 2004
Noris et al 2010
Caprioli et al2006,

Triggers for acquired aHUS

- Infection
- Drugs
- Malignancy
- Transplantation
- Pregnancy-associated
- Underlying medical conditions

Clinical and paraclinical manifestation

- Irritability ,Pallor,Edema,GE,Respiratory symp.,oliguria
- Triad of MAHA,Thrombocytopenia, **AKI**
- High LDH
- Hypertension
- Nl PT,PTT
- Nl coombs Test
- Nl ADAMTS 13 level
- C3,CFI,CFH↓ or not

Clinical manifestations

- **Extrarenal Manifestations**

✓ Neurologic: CNS and peripheral N. 8-48%(seizure, coma, hemiparesis,…)

✓ Gastrointestinal: diarrhea, vomiting, pancreatitis , hepatitis, GI bleeding

✓ Repiratory : pulmonary hemorrhage ,respiratory failure, ARDS

✓ Cardiovascular: cardiomyopathy, HTN, thrombosis, MI

✓ Eye: diplopia, blurred vesion ,retinal hemorrhage, blindness

✓ Skin: rash and peripheral gangrene

✓ Skeletal muscle : rabdomyolysis

Cassandra Formeck, Agnieszka Swiatecka-Urban.Ped Nephrol aug 2018

Genetic analysis for aHUS

- Genetic screening for mutation in CFH, CFI, MCP, C3, CFB, THBD, DGKE by direct sequencing analysis ,NGS

- CFH CFHRs by MLPA*

- **Multiplex ligation-dependent probe amplification*

Who should undergo genetic screening, when and why?

- **When**

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

  -Family history of non synchronous HUS

  -Pregnancy/post-partum-HUS

  -De novo post–transplant HUS

Genetic screening is required before KTx for aHUS

Who should undergo genetic screening, when and why?

Why?

- 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 KTx: choice of the donor, treatment schedule to prevent or treat post-transplant recurrence, decision of combined KLTx
- Further prospective studies are required to establish the safety of complement blockade treatment discontinuation, according to the genetic background

Treatment options in the pre complement blockade era

- **Plasma therapy (PE,PI)**

Intensive PE within 24hr of Dx and continued for the 1st mo and gradual tapering

❖ PE: Complete or partial remission (hematologic remission with renal sequelae)

- 78 % of aHUS episodes in children and 53 % in adults in the Italian cohort

- 48 % of children & 67 % of adults had died or reached end-stage renal disease (ESRD) at 3-year follow-up in French cohort

PE/PI for Tx

Ariceta GEuropean Paediatric Study Group for HUS (2009) Guideline for the investigation and initial therapy of diarrhea-negative HUS.Nephrol 24:687–696

Johnson S: An audit analysis of a guideline for the investigation and initial therapy of diarrhea negative aHUS. Pediatr Nephrol 29:1967–1978

Terminal complement blockade treatment (Eculizumab)

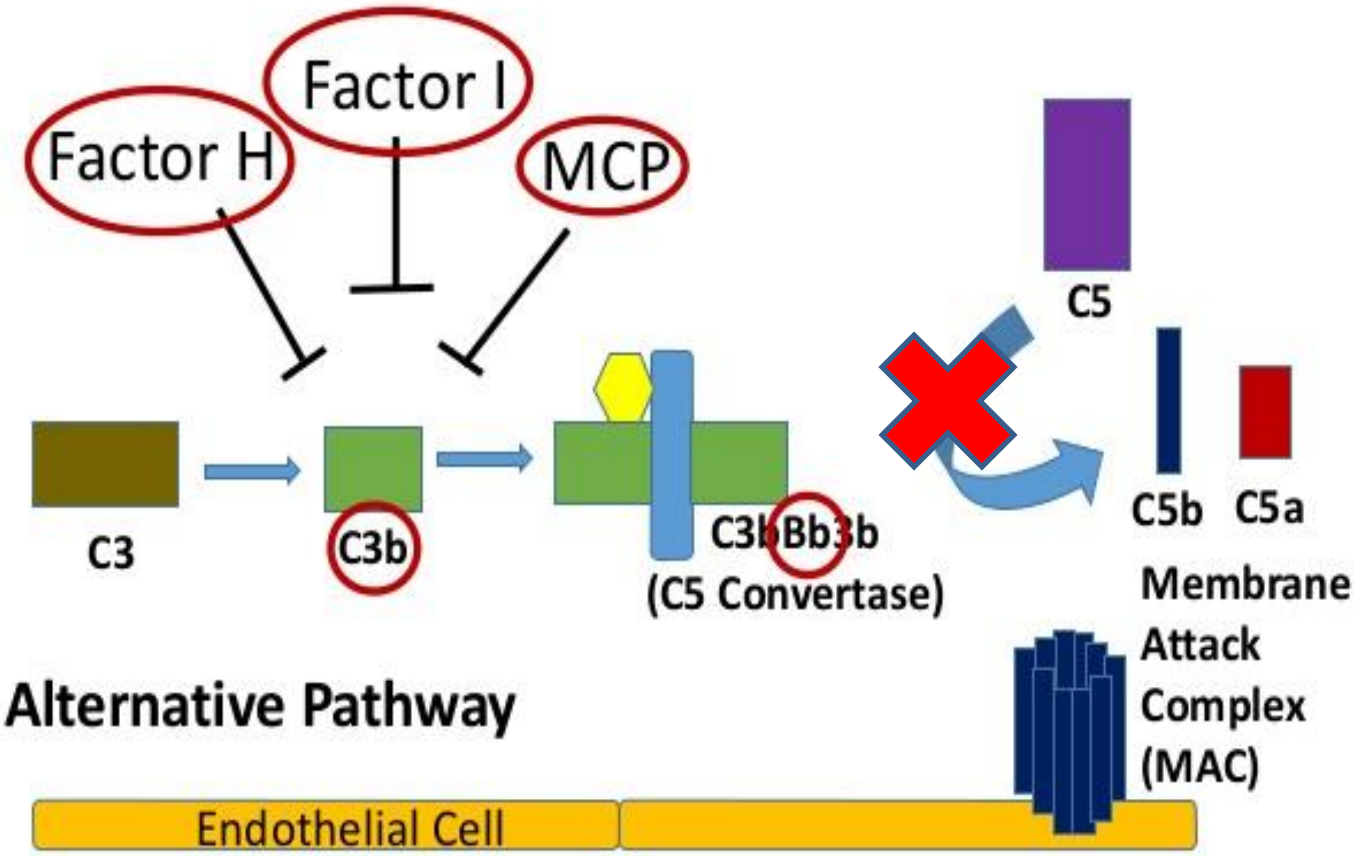
❖**Eculizumab (2011)**

A monoclonal humanized anti-C5 Ab, prevents C5 cleavage and the formation of C5a &C5b-9

Blocking the C5a pro-inflammatory and the C5b-9 pro-thrombotic consequences of complement activation

Eculizumab is approved for Rx of aHUS in USA & European Union ….

Site of Eculizumab Action



Eculizumab initial trials

1st trial 17 pt. resistant to PE/PI

platelet count normalized median:7 days(1-218)

LDH activity median of14 days (0–56 days)

After the first dose of Eculizumab and maintained in Rx period(2yrs)

The eGFR improved by 32 ml/min/1.73 m2

Only 2 pt was on dialysis

Gain in GFR was better in non-Tx than in Tx pt and with shorter delay

LegendreCM (2013) Terminal complement inhibitor eculizumab in atypical Hemolytic-uremic syndrome.N Engl J Med 368:2169–2181

Licht C, (2015) Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome: 2-year results from extensions of phase 2 studies. Kidney Int. 87(5):1061-73

Eculizumab initial trials

Two subsequent trials comprised 22 children and 41 adults

-55% children and 15%adults received Eculizumab without prior PE/PI,

- Complete TMA response with improved renal function after 26 wks of treatment in **64 % of children ,while 80 % of adults** had complete TMA response with preserved renal function over 1 year treatment duration

Renal function recovery was greater in the pediatric compared to the adult cohort (**64 ml/min/1.73 m2 versus 29.3 ml/min/1.73 m2** at week 26, respectively).

Only 9 % (2/22) of children&12 % (5/41) of adults required dialysis at 26 wks and 1 year of continued eculizumab therapy

Greenbaum LA,et al.(2013) Eculizumab inhibits thrombotic microangiopathy and improves renal function in pediatric atypical hemolytic uremic syndrome patients [Abstract]. J Am Soc Nephrol 24:821A–822A

Fakhouri F,et al.(2014) Eculizumab inhibits thrombotic microangiopathy,and improves renal function in adult atypical hemolytic uremic syndrome patients: 1-Year Update [Abstract]. J Am Soc Nephrol 25:751A

Clinical practice recommendations for patients with aHUS

- Eculizumab is 1st line treatment in children
- If possible within 24-48hrs of Dx
- If not available PE-----PI
- Anti-CFH Ab testing is the only complement investigation urgently needed

Eculizumab dosage regimen, standard therapy according to EMA/FDA

Wt. Category	Induction Phase	Maintenance Phase
>18yrs and Weight >40 kg	900 mg once a wk for 4 wks	1200 mg in wk 5,then 1200 every 2 weeks
30–40 kg	600 mg once a wk for 2 wks	900 mg in wk 3,then 900 mg every 2 wks.
20–30 kg	600 mg once a wk for 2 wks	600 mg in wk 3,then 600 mg every 2 wks.
10–20 kg	600 mg in wk 1	300 mg in wk 2, then 300 mg every 3 wks.
5–10 kg	300 mg in wk 1	300 mg in wk 2,then 300 mg every 3 wks.

Vaccination and Antibiotic Prophylaxis

- Treatment with Eculizumab is associated with life-threatening and fatal meningococcal infections

Tetravalent conjugate vaccines(anti-A, C, Y, W)+Anti-B vaccine
Also vaccination for S. pneumonia& H. influenza type b,

- **Methylpenicillin** twice daily :full dose for 2wks or as far as pt.is on Eculizumab and 2Mo after D/C

Treatment of anti-CFH Ab-associated HUS

- Anti-CFH antibody-associated HUS treated mostly with PE without immunosuppressants reported a poor outcome including:

Death in 9 %, relapses in 58 %, CKD in 39% and ESRD in 27%after a mean followup of 39 (range, 1–168) months

However, in a another cohort of children: Treatment with

PE, **immunosuppressants and corticosteroids** much better outcome

Dragon-DureyMA,et al. 2010Clinical features of anti-factor H autoantibody-associated HUS. J Am Soc Nephrol 21:2180–2187

Fremeaux-Bacchi V,et al (2013) Genetics and outcome of atypical hemolytic uremic syndrome:a nationwide French series comparing children and adults. Clin J Am Soc Nephrol 8:554–562

Kidney transplantation for patients with atypical HUS

Choice of the donor and practical issues for the prevention of atypical HUS recurrence after TX

Risk of Post-Tx recurrence is mostly determined by genetics and, in patients with anti-CFH antibodies, the anti-CFH antibody titer

Complete genetic screening and anti-CFH antibody assay are required before listing the patient for KTx

Post transplant Recurrence

In patients at high risk of post Tx recurrence, should prophylactic eculizumab treatment be applied or should the physician wait for recurrence to start eculizumab?

Prophylactic use

What is the place of combined LKTx in aHUS

Liver transplantation (LT) or combined liver–kidney transplantation(CLKT) in patients with severe aHUS and mutations of complement factors synthesized in the liver (CFH, CFB and C3) is the only option to cure aHUS

20 patients with CFH (n=18), CFB (n=1) or C3 (n=1) mutation with pre-op PE,PI and Eculizumab 16(80%) were cured

Saland J (2014) Liver–kidney transplantation to cure atypical HUS:still an option post-eculizumab? Pediatr Nephrol 29:329–332

REVIEW ARTICLES

Eculizumab in atypical hemolytic uremic syndrome: strategies toward restrictive use

Kioa L. Wijnsma & Caroline Duineveld & Jack F. M. Wetzels2 & Nicole C. A. J. van de Kar

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Pediatric Nephrology (2019) 34:2261–2277

Where Are We?
What Can We Do?

1-To have a registry of aHUS

2-To have a specific genetic lab assigned for aHUS

3-To try for availability of Eculizumab for aHUS

4-when available to have a committee of experts for decision about Eculizumab use

Take Home Message

- ✓ aHUS is a TMA caused by dysregulation of complement pathway
- ✓ Usually has a genetic background that is triggered in specific situations
- ✓ Genetic study is needed for patients with aHUS and ESRD before Tx
- ✓ On time diagnosis of aHUS in pts with TMA for early Rx
- ✓ Eculizumab is the treatment of choice if not available high dose PE
- ✓ The cost of Eculizumab is a barrier to its universal use