Peri- and Post-operative Evaluation and Management of Atypical Hemolytic Uremic Syndrome (aHUS) in Kidney Transplantation

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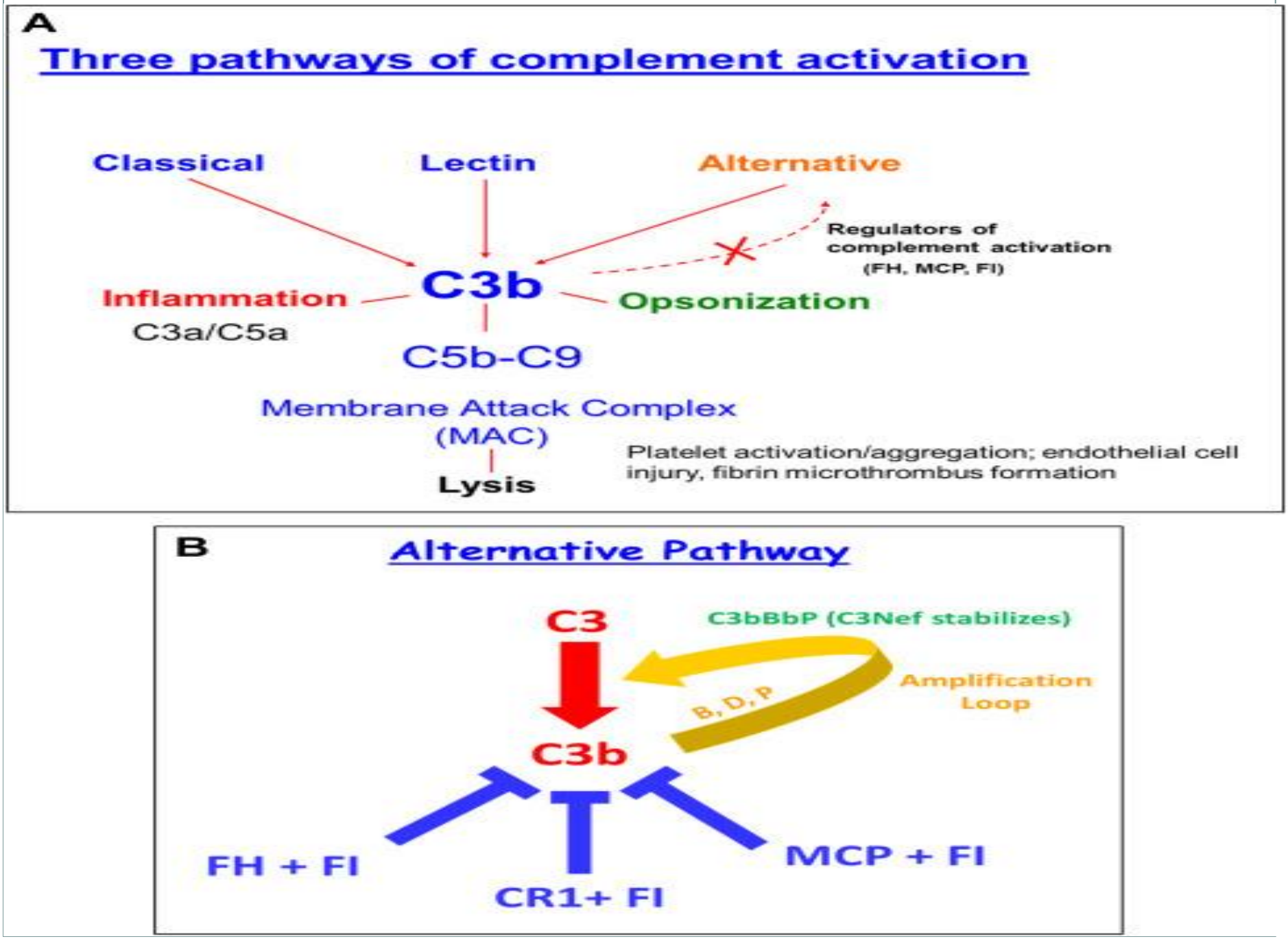
Introduction

- Atypical hemolytic uremic syndrome (aHUS) is a severe thrombotic microangiopathy characterized by over-activation of the alternative complement pathway.
- The etiology of the dysregulated complement system is commonly a genetic variant in one or more complement proteins as identified in 60%-70% patients.
- The risk of recurrence after a kidney transplantation is high and depends on the underlying complement abnormality.
- Over the past decade, advancements in the understanding of etiopathogenesis of aHUS and approval of the anti-complement drug, eculizumab, have allowed for successful kidney transplantation in these patients.

Complement dysregulation

- The most common - heterozygous, loss-of-function mutation in Factor H (FH), Factor I (FI), or membrane cofactor protein (MCP; CD46)—all regulators of the alternative pathway (AP).
- Gain in function of Factor B and C3.
- In these cases, the protein is generally (a) not synthesized and/or not secreted or (b) secreted into the blood in normal amounts but is dysfunctional.
- Disease penetrance is 50%.


A
Three pathways of complement activation
Classical
Lectin
Alternative
Regulators of complement activation (FH, MCP, FI)
Inflammation
C3a/C5a
C3b
Opsonization
C5b-C9
Membrane Attack Complex (MAC)
Lysis
Platelet activation/aggregation; endothelial cell injury, fibrin microthrombus formation
B
Alternative Pathway
C3
C3bBbP (C3Nef stabilizes)
Amplification Loop
B, D, P
C3b
FH + FI
CR1+ FI
MCP + FI

Complement Regulatory Proteins and Atypical Hemolytic Syndrome

Complement Protein	Synthesis Site (Distribution)	Frequency in aHUS (%)	Risk of ESRD (%) (Pre-Eculizumab)	Risk of Recurrence After Kidney Transplantation (%) (Pre-Eculizumab)
Factor H	Liver (serum)	20-30	50-70	75-90
MCP	Cells (wide distribution)	10-20	0-6	<20
Factor I	Liver (serum)	5-15	50	45-80
C3	Liver (serum)	5-15	60	50-60
Factor B	Liver (serum)	<5	50	40-70

Recommended Testing for Pre transplantation Evaluation for aHUS

- Serum C3 C4 CH50 and ADAMTS13.
- [C4 levels high in factor H auto Ab variant.].

- Normal C3 levels do not exclude mutations in complement regulatory proteins.
- Serum FH/FI/anti factor H auto Ab levels.

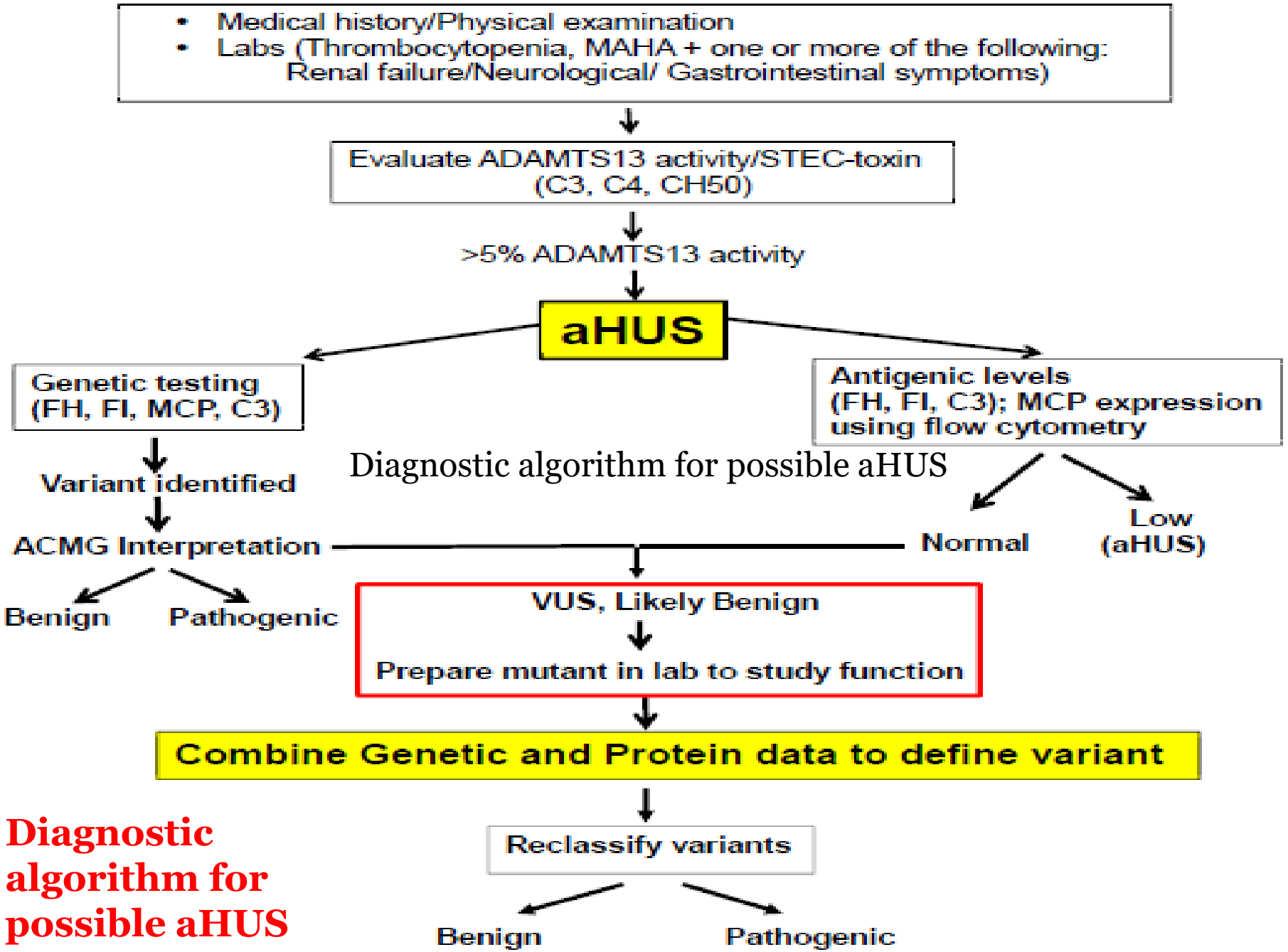
- MCP expression on leukocytes by flow cytometry.[detect 75%].

- Genetic testing : –

ADAMTS13,C3,CD46,CFB,CFH,CFHR1,CFHR2,CFHR3,CFHR4,CFHR5,CFI,DGKE,THBD.

Variants of uncertain clinical significance

- Only 50%of variants have known clinical significance.
- Genetic labs produce recombinant proteins, assess regulatory function and perform structural modeling of the variant protein.
- Reported as benign and pathogenic.
- Helps in pre transplant work up and determining need of prophylactic eculizumab.



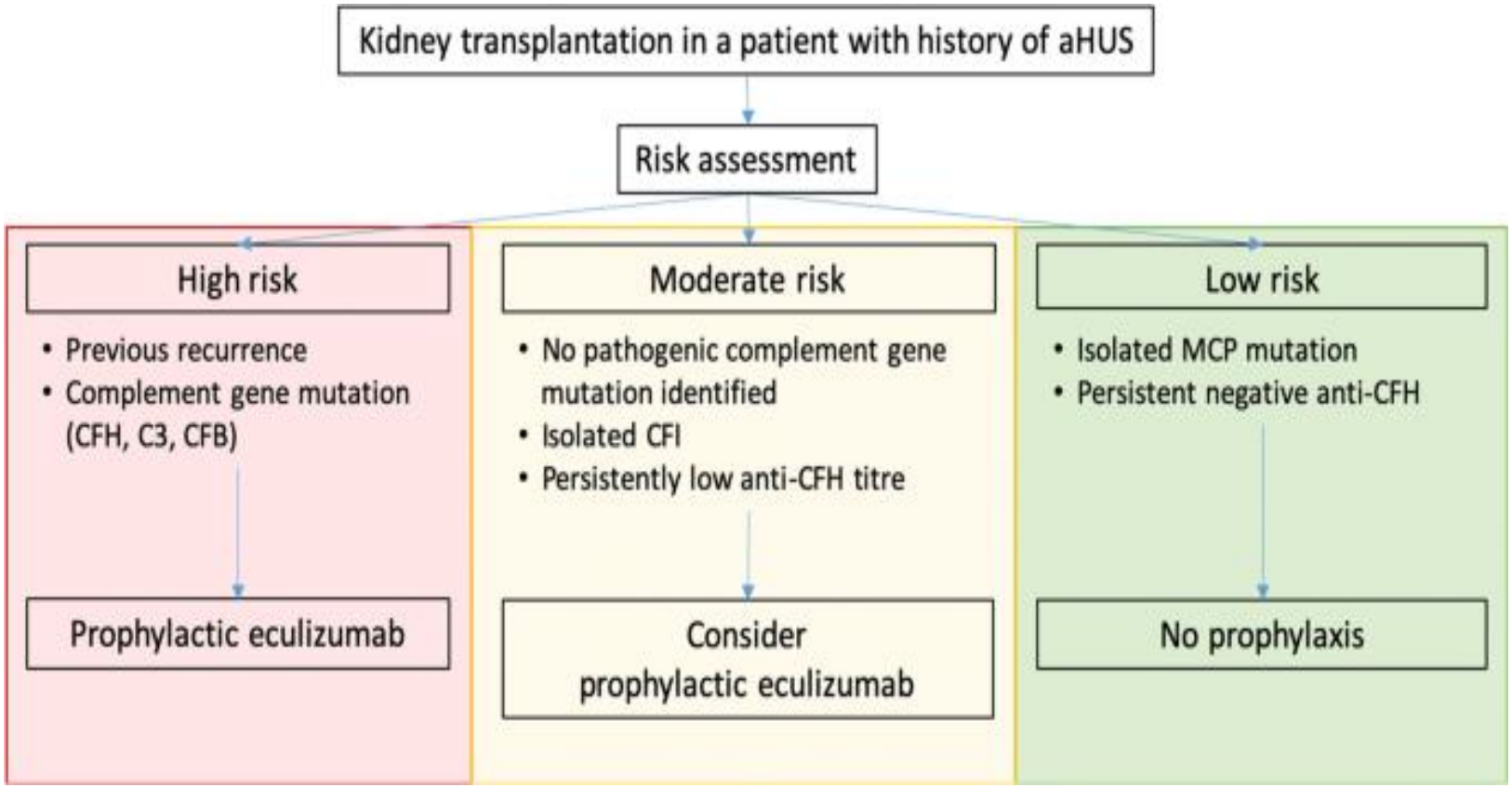
Diagnostic algorithm for possible aHUS

Diagnostic algorithm for possible aHUS

Live related donor

- Living-related donor kidney transplant is relatively contraindicated for patients with aHUS. This is primarily for donor safety **because nephrectomy may trigger TMA in the genetically susceptible donor.**
- Some patients may have **more than 1 mutation**.
- 1/3rd of patients with aHUS, genetic testing **does not reveal a variant** in the complement gene.
- Living-donor transplants could be considered with caution on a **case-by-case basis.**
- **Donor has to test negative for the pathogenic mutation.**

Risk assessment pre transplant



Preparing the Child with End-Stage Renal Disease for a Renal Transplant: the Pre-transplant Assessment
Chia Wei Teoh, Moira Korus, Armando Lorenzo & Valerie Langlois Current paediatrics reports volume 8, pages134–146JUNE (2020)

Eculizumab dosing

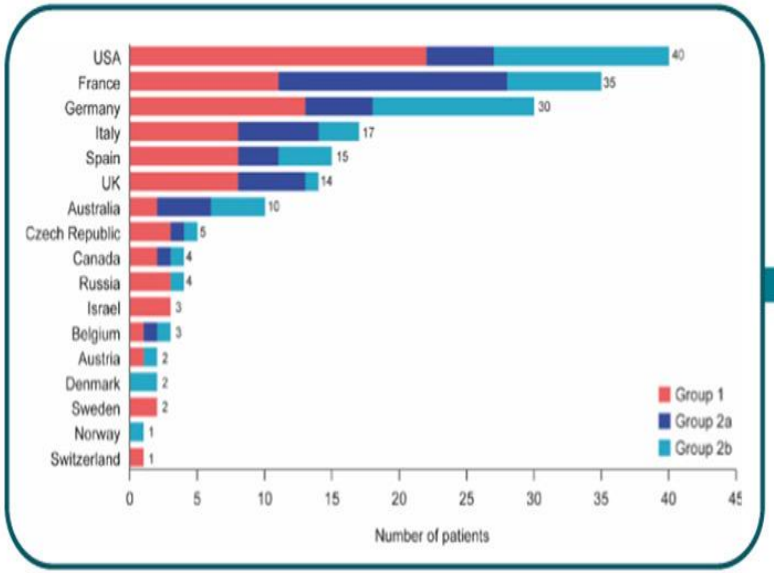
- In patients who are receiving a living-unrelated donor kidney, we administer eculizumab at 900 mg intravenously 24 hours before transplantation and on days 7, 14, and 21 after transplantation, followed by 1200 mg on week 5 and then every 2 weeks thereafter.

- In patients who are receiving a deceased-donor kidney, we administer eculizumab at 900 mg intravenously at the time of transplantation.

- Sideeffects:- HTN/headache/URTI/UTI/nausea/vomiting/diarrhea/anemia/leukopenia.

Eculizumab use for kidney transplantation in patients with a diagnosis of atypical hemolytic uremic syndrome

Patients receiving transplant and eculizumab in Global aHUS Registry, N=188



Patients on dialysis post-transplant

Group 1
Diagnosis prior to transplant, eculizumab before transplant
n=88 (47%)
→ **n=6 (7%)**

Group 2a
Diagnosis prior to transplant, eculizumab after transplant
n=52 (28%)
→ **n=12 (23%)**
AHR=2.30

Group 2b
Diagnosis after transplant, eculizumab after transplant
n=48 (26%)
→ **n=29 (60%)**
AHR=4.62

Graft function post-transplant

Median eGFR within 6 months was significantly better in:

Group 1
60.6 ml/min/1.73m^2

Compared to:

Group 2a
31.5 ml/min/1.73m^2
***p*=0.004**

and

Group 2b
9.6 ml/min/1.73m^2
***p*=0.0001**

CONCLUSION:

Delayed diagnosis of aHUS and delayed treatment with eculizumab post-transplant leads to inferior outcomes

KI REPORTS
KIReports.org
Siedlecki et al. *Kidney Inter Rep.* 2019

The use of highly individualized complement blockade revolutionized post-transplant outcomes and renal epidemiology of aHUS

METHODS

Study 1: transplant outcomes

Adult aHUS patients
- Complement work-up
- Kidney transplantation after 01/01/2007

↓

126 Kidney transplantations
- Risk stratification
- Tailored eculizumab prophylaxis

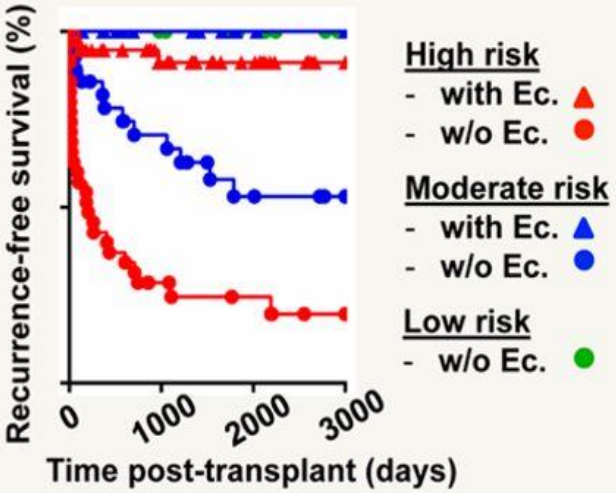
Study 2: population-based

Adult aHUS patients
- Complement work-up
- Alive between 01/01/2007 and 01/01/2016

↓

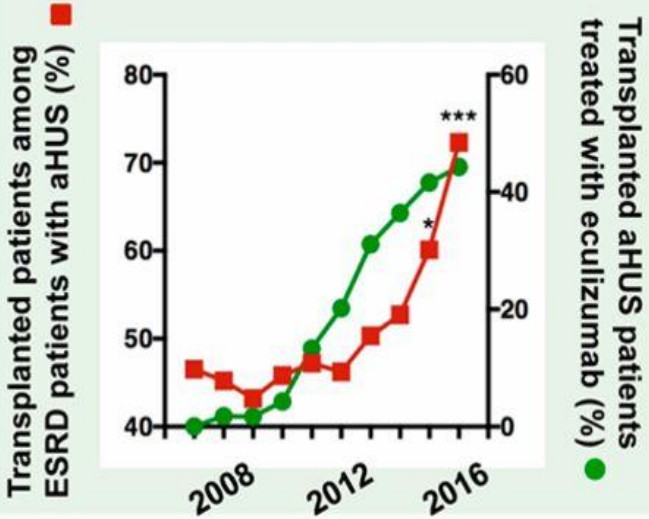
Renal status over time in 397 aHUS patients

Study 1: Post-transplant outcomes according to risk stratification and eculizumab (Ec.) prophylaxis



OUTCOME

Study 2: Changes in the aHUS epidemiology at a nationwide level



CONCLUSION:

These studies support the use of eculizumab prophylaxis in those for whom medical history and complement investigations predict a high and moderate risk of post-transplant recurrence.

doi: 10.1681/ASN.2019040331

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Meningococcal Vaccine

- Life threatening Neisseria Meningitidis infection is of concern.
- Meningococcal conjugate or MenACWY vaccines and Serogroup B meningococcal or MenB vaccines to be given two weeks before transplant.
- A booster dose of MenACWY given every five years till duration of complement inhibitor.

Transplant protocol without eculizumab [low risk cases]

- ATG > Basiliximab induction.
- Triple immunosuppression- TAC/MMF/PRED.
- Low dose tacrolimus is preferred to keep trough level around 5-7.
- Injectable methyl prednisolone 500 mg pre transplant.
- Eculizumab only if recurrence.
- Five sessions of plasmapheresis pre transplant and two sessions of plasmapheresis post transplant.

Case series from Netherlands

- 17 pts of atypical HUS with 16 carrying genetic variants- CFH/CFI/C3/C5.
- 5 /17 patients had previous allograft loss due to recurrent aHUS.

- Induction –BASILIXIMAB.
- NO ECULIZUMAB.

- Low dose TAC/MMF/PRED. Strict monitoring of BP.
- Patients were trained to report HTN/hematuria/proteinuria/deranged renal function at home.

- At 25 months follow up- average Cr was 1.2 .
- One graft loss due to recurrence which could be salvaged with eculizumab therapy.

Post transplant Monitoring for aHUS

Immediate Posttransplant (During Hospitalization)	Daily, CH50/AH50 Before Eculizumab Administration for the 1st Four Doses
Up to 6 months	Weekly
6-12 months	Biweekly
After 12 months	Monthly

Complete Blood Count, Renal Panel, Urinalysis, Lactate Dehydrogenase,Haptoglobin.

A peripheral smear should be obtained in addition to the above if there is any concern for recurrence.

Recurrence

- Patients with recurrent aHUS usually present within 1 year and often within days to weeks.

- Triggers for recurrence after transplant:-

A] ischemia-reperfusion injury.

B] immunosuppressive drugs (calcineurin and mTOR inhibitors),

C] antibody-mediated rejection.

D] infections (cytomegalovirus, BK virus, upper respiratory or gastroenteritis).

Recurrence

- Risk of recurrence is high in patients carrying a pathogenic mutation in any of the complement proteins except MCP.
- The recurrence rate is low in patients with isolated MCP mutations because the allograft expresses normal membrane bound MCP
- Patients at moderate risk of recurrence include those carrying a VUS in any protein and genetic variant has not been identified.
- Low risk of recurrence also include those who have been successfully treated for removal of FH autoantibodies.

Recurrence treatment

- Eculizumab 900 mg weekly for four weeks followed by 1200 mg at week 5 and thereafter every two weeks and plasmapheresis.
- Few reports of replacing tacrolimus with belatocept
- In high risk cases give lifelong treatment.
- In low risk cases give for 24 months and assess and consider stopping Eculizumab.

De Nova a HUS after kidney transplant

- 1-5% cases reported.
- In one series complement variants were identified in 29% patients.
- Patients may carrying a low risk of a-HUS , risk multiplies after transplant due to multiple factors like reperfusion injury / ABMR /infections .

The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naive to complement inhibitor treatment

Who was tested?

56 patients with aHUS

Reduced hemoglobin

Platelets <150 x 10^9/L

Increased Scr

Increased LDH

All patients with acute TMA

88% with eGFR <29

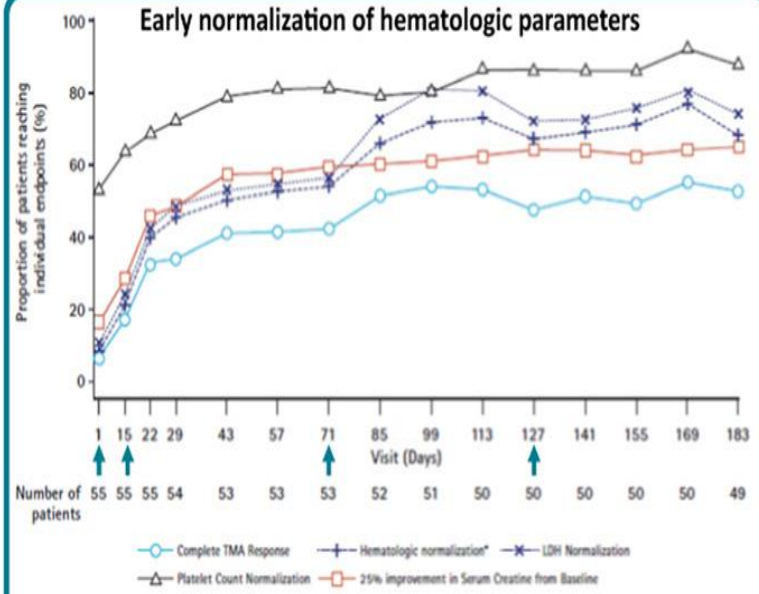
52% on dialysis

What was done?

Ravulizumab induction dose — Day 1

Ravulizumab maintenance doses — Day 15, Day 71, Day 127

Complete TMA response was achieved in 54% of patients and 59% of patients on dialysis at baseline came off dialysis by Day 183



Safety

No unexpected adverse events identified

No meningococcal infections observed

Four deaths unrelated to ravulizumab treatment

CONCLUSIONS:

- Ravulizumab provided immediate and complete inhibition of C5 (defined as free C5 <0.5µg) sustained over the 8-week dosing interval
- Substantial improvement was achieved in platelet count, LDH, serum creatinine and renal function and no unexpected adverse events were identified
- The results of this study support the use of ravulizumab at 8-weekly dosing intervals in adult patients with aHUS

Rondeau, 2019

ISN kidney INTERNATIONAL
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