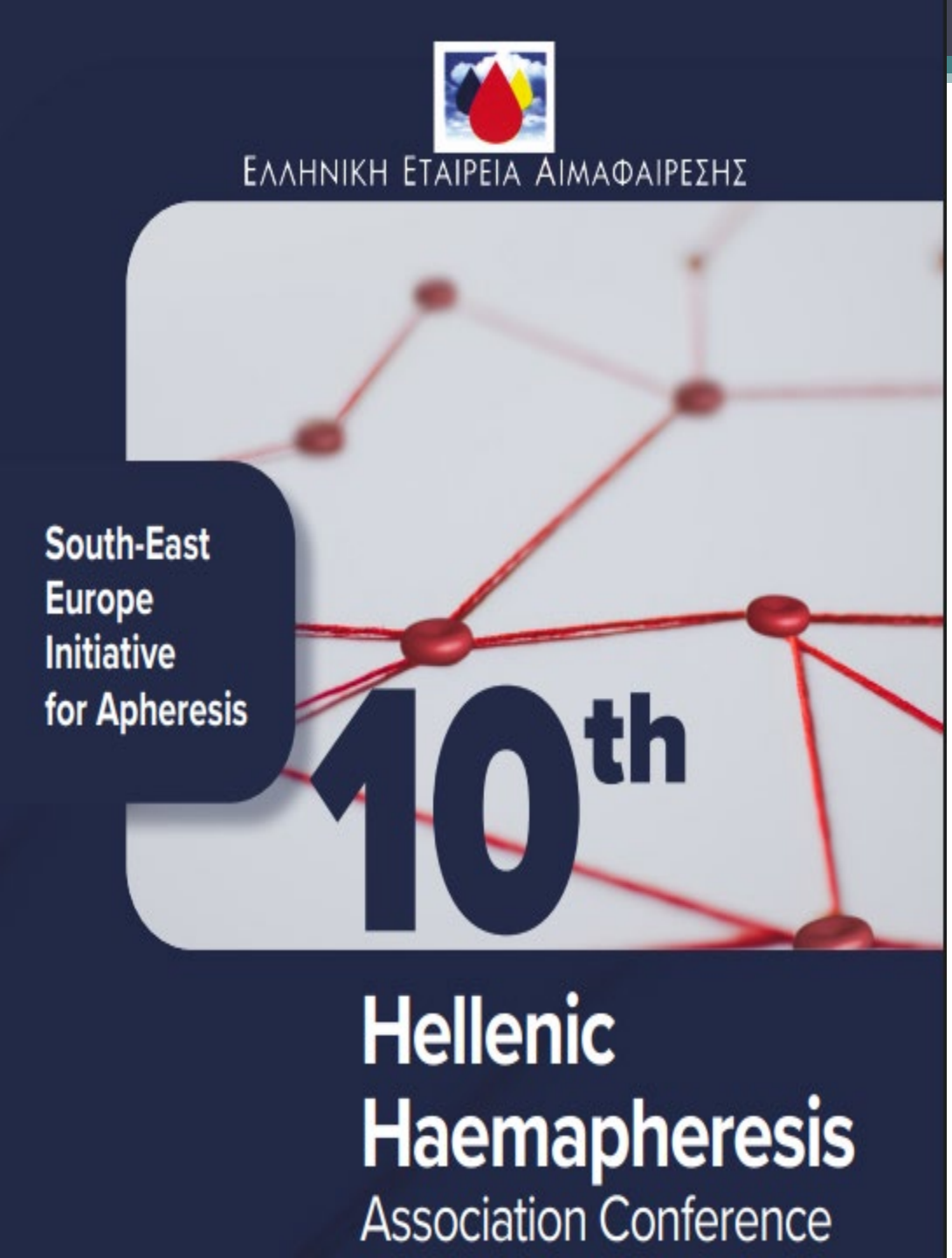

IS THERE STILL A ROLE FOR PLEX IN aHUS

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CASE REPORT

- 32-year old  , 2nd pregnancy, 26 weeks, history of **diarrhea for past 6 days (one bloody and mucousy stool)-** presented on **friday after working hours**

- First pregnancy normal, intermittent sinusitis, otherwise healthy

Urine	**+++prot and Er, 1 hyaline and 3-4 granular casts**	**Ref. range**
sCr	↑ 168… 219	53-97
Hb	↓ 117	119-157
PLT	↓ 43	158-424

CASE REPORT

- **Nephrologist suspected TMA** (HUS/TTP, PE/E and HELLP less likely), no evidence of systemic disease or infection (except for diarrhea) with further suggestions:

Recommendations for diagnostics (completed within 2 weeks)
standard lab tests including coagulation tests, serum immunoglobulins, peripheral blood smear, Coombs test, Hantan and Leptospirosis serology, blood and urine culture, swabs, hepatitis tests, sputum tests, swabs, COVID-19, haptoglobin, immunological tests including C3 and C4 complement levels…

- Referred and admitted to the Clinic for Gynecology and Obstetric

- **Multidisciplinary management and monitoring**

CASE REPORT

Worsening of the lab tests the next day	
Urine	++ prot
sCr	**↑242**
PLT	**↓33**
Haptoglobin	**<0.07**
COOMBS	**Neg**
CRP	46.9

- **Schistocytes present in peripheral blood smear**
- **Dg of TMA confirmed**
- Diarrhea improved but still present
- Testing for Shiga toxin not available…
- **No fetal or placental abnormalities**

- **Nephrologist: possible STEC-HUS or pregnancy-associated TMA/aHUS or TTP**
- AKI progressing
- **Mild hypertension, preserved diuresis but mild congestion**
- **Transient headaches** (subsequent **brain MRI normal**)
- **TTP not excluded or confirmed** (results of complement parameters sent abroad pending)

CASE REPORT

- Transffered to the ICU
- Initiation of **PLEX** daily and **HDF** with adjusted ultrafiltration
- Gradually reduced UF due to the clinical reduction of hypervolemia

CASE REPORT

- At the same time, **methyprednisolone was introduced** (initially in a dose recommended by hematologist 40 mg than the next day 60 mg)
- Nephrologist recommended dosage uptitration to 250 mg (3 days with a slight tapering while waiting for the test results - 125 mg …1 mg/kg - 80 mg… 60 mg and than gradually to the maintenance dose of 10 mg
- **IVIG** due to ↓globulins (11 g/L) and as an immunomodulatory Th
- Daily **heparin** with PEX and HDF

CASE REPORT

- Still waiting for complement results…
- **Kidney injury persists despite PEX, MP, IVIG and HDF**
- Had to receive **blood and even platelet transfusions** on couple of occasions (**recommended by the hematologist** 2x 8 doses due to the drop of platelets below 20)
- Nephrologist **initiated procurement procedure of anti-complement therapy** while waiting for the test results
- Vaccination for Meningococcus

CASE REPORT

- As for test results…
- **Immunology test all negative, except for initially normal than reduced C3 (0.55; ref 0.9-1.8) and C4 (0.1; ref 0.1-0.4)**
- **No evidence of infection** (testing for shiga toxin not available at the moment)
- After substantial subjective and partial clinical improvement**, transferred from ICU to** the **Department of NDT** of the Clinic for Internal Diseases by the decision of the MDT

CASE REPORT

- In the meantime, complement results from abroad started to arrive…
- **ADAMTS13 activity severely decreased, but not deficient, TTP is not probable**
- Haptoglobin deficient, hemolysis is supported
- C3 and C4 decreased, suggesting infection or autoimmune disease in the background- not proved, even repeated
- **If aHUS can clinically be verified and kidney failure persists, then complement inhibitory therapy should be considered.**
- **In the first sample** decreased Factor B level and deficient haptoglobin was observed. **Terminal pathway activation marker not elevated, anti FH Ab negative.**
- **In the second sample** low level of **complement factors and regulators are observed, without overactivation of the terminal pathway**
- **Complement dysregulation with overactivation was not shown, genetic testing was not done**

CASE REPORT

- **Gradual recovery of the kidney function and hemolysis parameters- <u>overall 9 PE and HDF</u>**

sCr	72
Urine	+ prot + Er, no casts
Hb	84
PLT	96
Haptoglobin	gradually increasing to normal values
LDH	440 →293

- **No signs of fetal or placental abnormalities**
- **<u>Liver function tests normal all the time</u>**
- **Patient subjectively and clinically better**

CASE REPORT

- **Dillema…**
- **‘Complement dysregulation with overactivation was not shown‘.**
- **Watchful waiting or anticomplement therapy?**

- Could this be the case of **STEC HUS** that took **atypical course during pregnancy with complement dysregulation but without overactivation, and** spontaneously or with applied therapy **entered remission?**

- **Consultation with the expert…**

CASE REPORT

- **Expert opinion:**
- Careful watch & wait is the best option at the moment
- Infection-associated TMA episode? most probably non-verotoxin. aHUS is less likely
- In case of new flare of TMA without an alternative explanation- complement inhibitory therapy is absolutely indicated and genetic would be done!

CASE REPORT

- Discharged home after 30 days of hospital treatment
- Close monitoring by the OB-GYN and nephrologist
- Pronison in maintenance dose of 5 mg, discontinued after the birth
- Normal kidney function; the rest of the pregnancy uneventful
- Vaginal delivery without complications and gave birth to a healthy baby
- Normal kidney function and other blood tests in the postpartum period (2 years now)
- Thanks to this case, complement inhibitory therapy placed on operative cantonal list for adult aHUS cases

Thrombotic microangiopathy (TMA)

- Heterogeneous group of disorders characterized by microvascular thrombosis and end-organ damage
- Multiple etiologies, with pregnancy and postpartum being a high risk
- pTMA results in high mortality (~4.5 x) and morbidity (81% requiring dialysis and 46% ESKD)
- Identifying specific form of p-TMA is critical for appropriate and timely management

Urra et al. Kidney Int. 2024
Fremeaux-Bacchi V et al. Clin J Am Soc Nephrol. 2013
Chen HY et al. Int J Gynecol Obstet. 2023
Lim MY et al. Obstet Gynecol. 2023
Frimat M et al. Front Med (Lausanne). 2024

› Int J Gynaecol Obstet. 2023 Dec;163(3):940-947. doi: 10.1002/ijgo.14918. Epub 2023 Jun 14.

Long-term survival and renal outcomes of thrombotic microangiopathy in pregnancy: A retrospective cohort study

Hsin-Yu Chen [1 2], Jin-Chung Shih [3], Meng-Han Tsai [4], Ching-Hu Chung [5]

Affiliations + expand

PMID: 37317480 DOI: 10.1002/ijgo.14918

Abstract

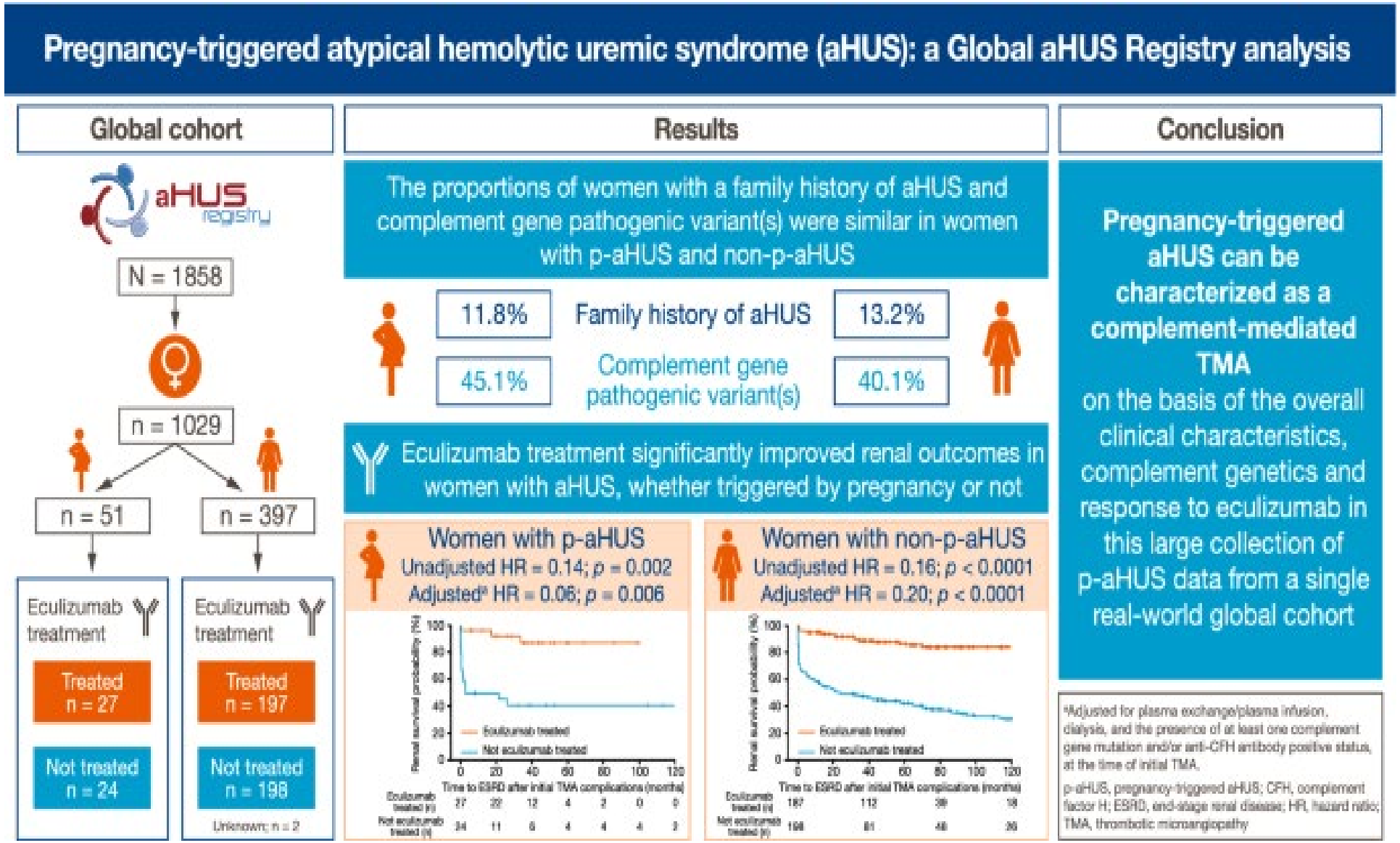
Objective: Thrombotic microangiopathy (TMA) in pregnancy can rapidly progress, leading to severe morbidities. This study aimed to compare baseline demographics and clinical outcomes between pregnant women with and without TMA.

Methods: Using the National Health Insurance Research Database, 207 patients with pregnancy-related TMA from January 1, 2006 to December 31, 2015 were enrolled. Their data were compared with a 1:4 propensity score-matched cohort of 828 pregnant women without TMA to evaluate mortality and end-stage renal disease (ESRD) risks. Cox proportional hazards models were used to estimate the adjusted hazard ratio and 95% confidence intervals.

Results: A total of 1035 participants were included. The risks of mortality and ESRD were 4.46 and 5.97 times higher for the TMA cohort, respectively. Subgroup analysis revealed higher mortality and ESRD risks in patients with TMA aged >40 years with a history of hypertension, stroke, cancer, concomitant stroke, malignant hypertension, or gastroenterocolitis than in the matched cohort.

Conclusion: Pregnant patients with TMA, especially those older and with comorbidities and organ involvement, faced increased mortality and ESRD risks. Physicians should collaborate with obstetricians throughout the prenatal and postpartum periods for these patients.

Keywords: end-stage renal disease; pregnancy; survival; thrombotic microangiopathy.



Fakhouri et al. Journal of Nephrology, 2021

Incidence of pCM-TMA in 1 in 25,000 pregnancies accounting for 7% of all TMA cases

KI REPORTS
KIReports.org
CLINICAL RESEARCH
Kidney International Reports (2025) 10, 3943–3954

Shiga Toxin–Producing *Escherichia coli*–Associated Hemolytic Uremic Syndrome in Adult Kidney Transplant Recipients

Manal Mazloum[1,2], Pierre Trémolières[1,2], Nesrine Baili[3], Cédric Rafat[4], Hannah Kaminski[5], Nassim Kamar[6], Edouard Lefevre[7], Dominique Bertrand[8], Charlene Levi[9], Sophie Chauvet[10], François Provôt[11], Roxane Gamot[12], Pierre-François Westeel[13], Sophie Caillard[14], Nicolas Bouvier[15], Fatouma Touré[16], Simon Ville[17], Moglie Le Quintrec[2], Dany Anglicheau[1], Rebecca Sberro-Soussan[1], Frank Martinez[1], Christophe Legendre[1], Julien Zuber[1], Stéphane Bonacorsi[18,19], Patricia Mariani[19], Aurélie Cointe[19] and Anne Scemla[1]

Introduction: Shiga toxin (Stx)-producing *Escherichia coli (E coli)*-associated hemolytic uremic syndrome (STEC-HUS) is an acquired form of thrombotic microangiopathy (TMA) caused by food and waterborne infection. It remains the leading cause of acute renal injury (AKI) in children. In adults, STEC-HUS is less common but often more severe. Data on STEC-HUS in kidney transplant recipients (KTRs) are limited.

Methods: We conducted a retrospective study involving adult KTRs diagnosed with STEC-HUS between January 2012 and April 2022 across 15 French nephrology centers. We aimed to characterize the clinical, biological, and microbiological features of STEC-HUS in this population, its management, and outcomes.

Results: A total of 35 adult KTRs were included. The annual incidence was estimated at 14.4 cases per 100,000 KTRs. Six and 29 patients presented with localized intrarenal or systemic TMA, respectively. The median time from transplantation to STEC-HUS diagnosis was 3 (1.2–6.2) years and the mean age at diagnosis was 57 ± 13 years. Neurological and cardiac complications occurred exclusively in patients with systemic TMA. AKI and significant proteinuria were observed in 89% and 94% of patients, respectively. All patients requiring dialysis exhibited systemic TMA (38%). Treatment included azithromycin, eculizumab, and conversion from calcineurin inhibitors (CNIs) to belatacept. Graft loss and mortality rates were 26% and 9%, respectively.

Conclusion: This study highlights that STEC-HUS represents a serious complication in KTRs, significantly impairing renal and overall survival. It should be systematically considered in cases of *de novo* posttransplant TMA, whether in the absence of prodromal diarrhea or in localized intra-renal presentations.

Table 3. Management at diagnosis of STEC-HUS

Characteristics	Localized TMA (n = 6)	Systemic TMA (n = 29)	All patients (N = 35)	P-value[a]
Hospitalization	2/6 (33%)	29/29 (100%)	31/25 (89%)	0.003
Length of hospital stay (d)	6 (2–10)	23 (15–39)	22 (14–38)	0.04
Change in immunosuppression	4/6 (67%)	19/29 (70%)	23/35 (66%)	0.99
CNI withdrawal	4/6 (67%)	15/29 (52%)	19/35 (54%)	0.67
Switch CNI-belatacept	4/6 (67%)	8/29 (28%)	12/35 (34%)	0.15
Antibiotics	4/6 (67%)	20/29 (69%)	24/35 (69%)	0.99
Azithromycin	4/6 (67%)	12/29 (41%)	16/35 (46%)	0.38
Other antibiotics	0/6 (0%)	8/29 (28%)	8/35 (23%)	
Eculizumab	2/6 (33%)	12/29 (41%)	14/35 (40%)	0.99
Plasmapheresis	0/6 (0%)	11/29 (38%)	11/35 (31%)	0.15
Renal replacement therapy	0/6 (0%)	11/29 (38%)	11/35 (31%)	0.15
Red blood cell transfusion	1/6 (17%)	14/29 (48%)	15/35 (43%)	0.21
Platelet transfusion	0/6 (0%)	1/29 (3%)	1/35 (3%)	0.99

Table 4. Outcome data

Characteristics	Localized TMA (n = 6)	Systemic TMA (n = 29)	All patients (N = 35)	P-value[a]
Outcome at 3 mo				
Serum creatinine level, mg/dl	2.4 (1.9–2.4)	1.9 (1.3–3.0)	2.0 (1.4–2.4)	0.18
UPCR, g/g	1.5 (0.3–3.3)	0.8 (0.2–1.3)	0.9 (0.3–2.0)	0.46
Last follow-up				
Follow-up time (mo)	47 (16–55)	21 (5–47)	22 (6–48)	0.25
Serum creatinine level, mg/dl	2.1 (1.9–3.1)	1.6 (1.2–1.9)	1.8 (1.3–2.2)	0.04
UPCR, g/g	0.7 (0.5–7.7)	0.5 (0.2–0.9)	0.5 (0.2–1.0)	0.17
Death	0/6 (0%)	3/29 (10%)	3/35 (9%)	0.99
Graft loss censored for death	0/6 (0%)	9/29 (31%)	9/35 (26%)	0.30
Transplantectomy (refractory TMA)	0/6 (0%)	3/29 (10%)	3/35 (9%)	0.99
Acute rejection	0/6 (0%)	1/29 (3%)	1/35 (3%)	0.99

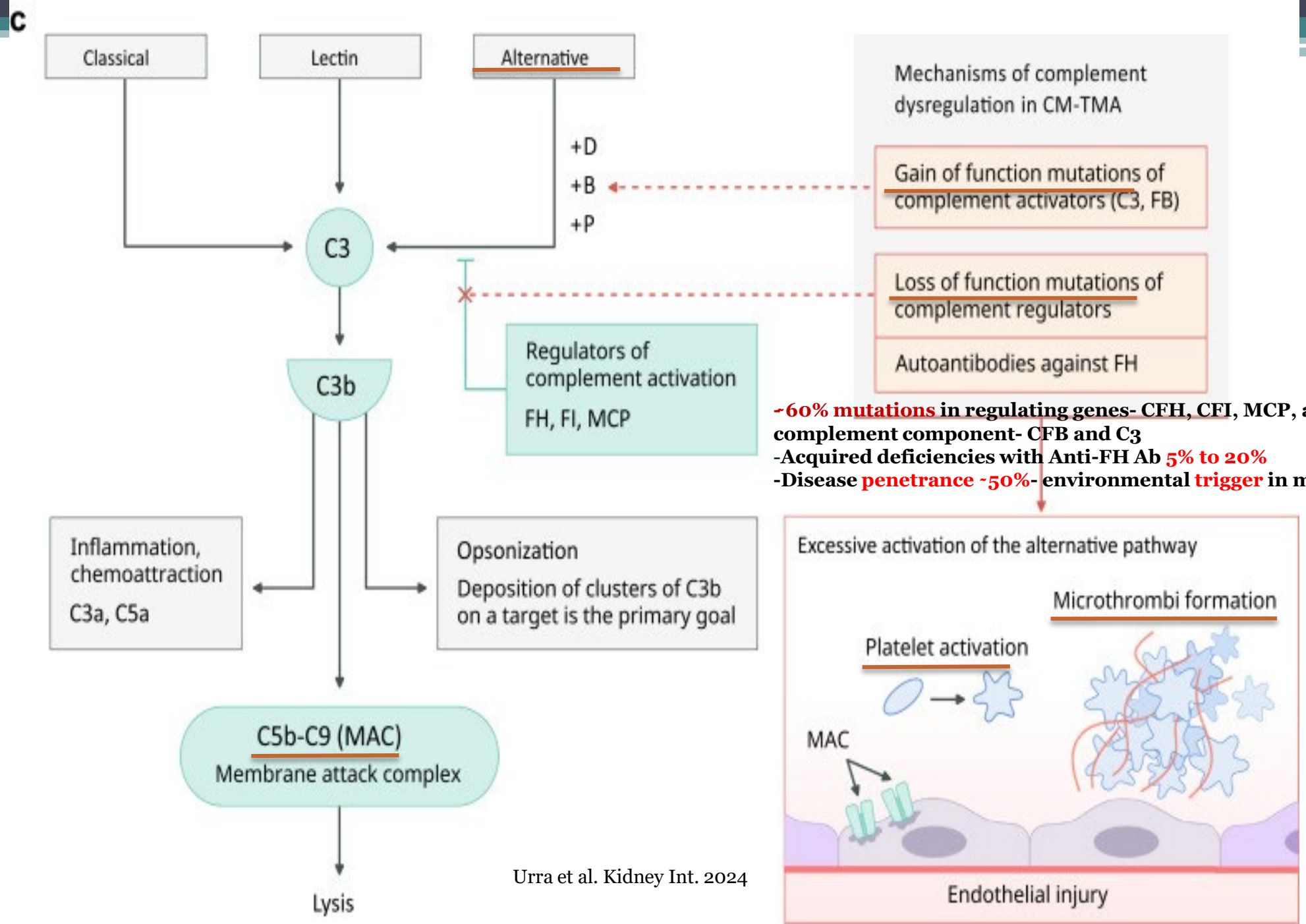
CONCLUSION

To the best of our knowledge, our study is the largest case series of STEC-HUS in adult KTRs ever reported, showing that STEC-HUS is a severe and not so rare complication in this population with an annual incidence 14 times higher than observed in children. We recommend systematic screening of STEC-HUS in any case of *de novo* posttransplant TMA, including in the absence of prodromic diarrhea or in patients with localized intrarenal TMA. Systemic TMA was associated with higher rates of graft loss and death. We hope our findings will likely pave the way for larger clinical studies aiming at identifying prognostic factors and a standardized therapeutic strategy in the specific population of KTRs.

CM-TMA

- CM-TMA results from overactivation of alternative pathway of complement
- Incidence ~1-2 cases PMP for adults aged~18 years ?
- Exact prevalence of aHUS unknown: 2.4-9.4 per million among aged <20 and 4.9 per million in all ages

Gupta M et al. Pregnancy Hypertens. 2018
Tseng et al. JFMA. 2023



~60% mutations in regulating genes- CFH, CFI, MCP, and genes of complement component- CFB and C3
-Acquired deficiencies with Anti-FH Ab 5% to 20%
-Disease penetrance ~50%- environmental trigger in most cases

Urra et al. Kidney Int. 2024

- aFH Ab associated aHUS unique entity occurring at any age, more prevalent in pediatric population
- Up to~20% caused by anti-CFH (aFH) Ab (24% in children and 19% in adults with aHUS)
- Some have genes encoding CFH-related proteins (CFHR1-5) and usually other genetic abnormalities
- Ab have impairing effect on regulatory function of FH causing dysregulation and overactivity of complement pathway
- Imperative to diagnose aFH Ab qickly and to provide timely treatment

Shawky et al. Int J Nephrol. 2021
Raina et al. Front. Immunol. 2022

Genetic Testing in aHUS May Inform Long-term Patient Outcomes

Genetic Abnormality	Frequency in Patients with aHUS	ESRD or Death within 3 to 10 Years of Diagnosis, % of Patients	Subsequent Disease Manifestation Post Transplant, @ of Kidney Grafts
CFH mutations	20%-52%	66%-80%	64%-90%
CFH autoantibodies and/or CFHR1-3 deletions	5%-10%	30%-63%	20%-29%
CFI mutations	4%-10%	50%-72%	45%-80%
THBD mutations	3%-10%	54%-60%	100% (1/1)*
C3 mutations	2%-10%	56%-67%	40%-70%
CFB mutations	1%-4%	70%	100% (3/3)*
Isolated heterozygous MCP mutations5	6%-15%	6%-38%*	0%-20%
DGKE mutations	~27% of patients diagnosed at≤1 year of age	46% (6/13)*	0% (0/3)*
CFH or MCP risk haplotypes	CFH-H3 : 31% MCPggaa0 : 44%		
No identified mutation	30%-50%	32%-50%	59% (17/29)*

Foonotes: *Plasminogem (PLG) mutations have not been included in this table because the outcomes of patients with aHUS and PLG mutations have not been reported**; *The ranges are based on kidney grafts that were affected by TMA manifestations. Some patients received multiple grafts.**, (n/N) of patients from one study.*, *The majority of patients with aHUS and MCP mutations studied in large cohorts had isolated heterozygous mutations. In one study, the rate of ESRD or death at 5 years of patients with aHUS and MCP mutations varied between adults and childre: 63% (5/8) of patients >16 years of age compared with 17% (2/12) of patients <16 years of age, X2 test P=0.03% (n/N) of patients from one study. 1% (n/N) of kideny grafts that failed by 1 year post transplant.

References 1. Noris M, Chin J Am Soc Nephrol 2010, 5 1844-1859 2. Noris M. N Engl J Med 2009, 361 1676-1687. 3. da Cordobs S. Semin Thromb Hemost 2014, 40:422-430

aHUS/c-TMA causes:

-50% of ESRD and

-25% mortality

Prognosis depends on:

-delay of therapy

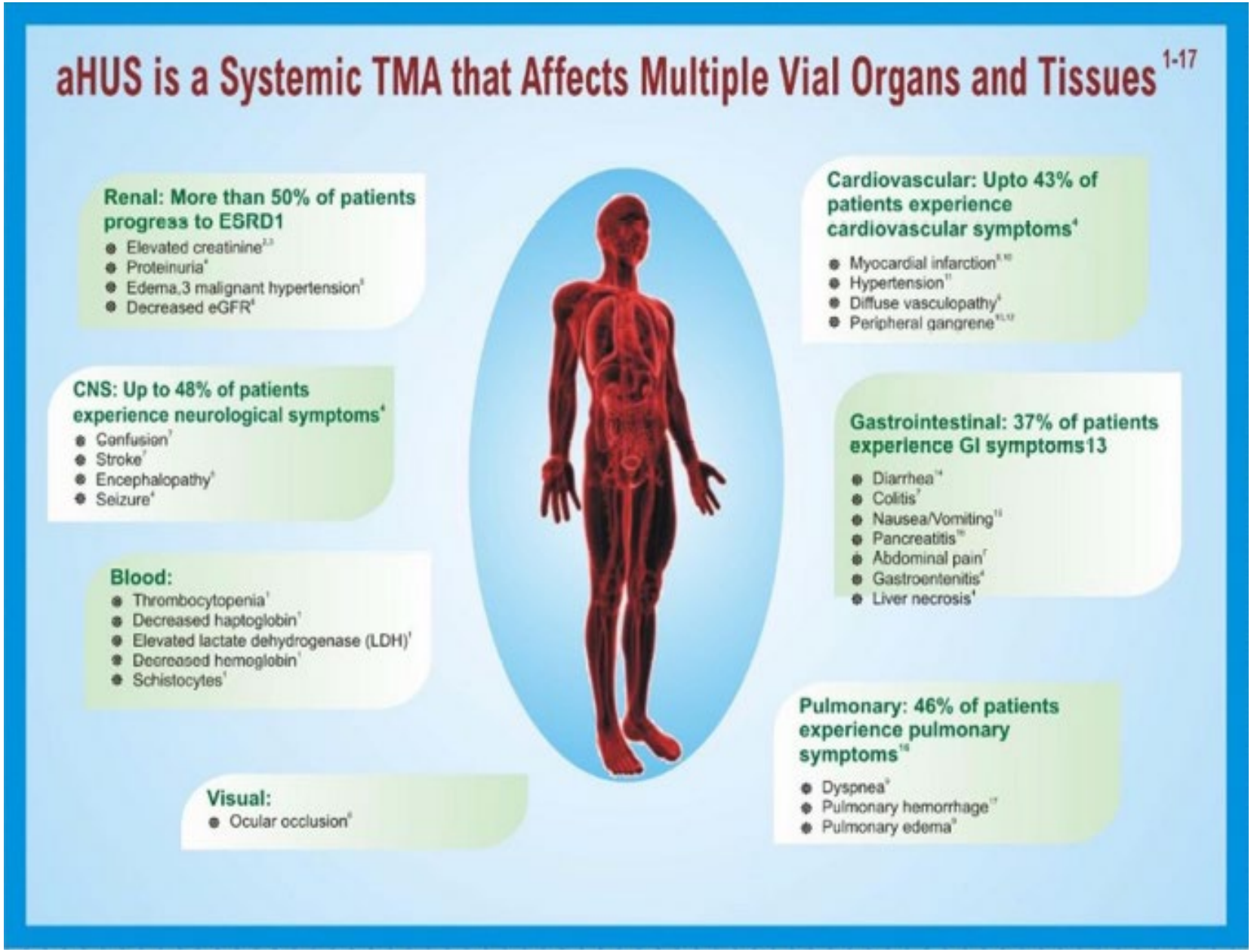
-severity and extrarenal involvement

Yerigeri et al. Journal of Multidisciplinary Healthcare. 2023

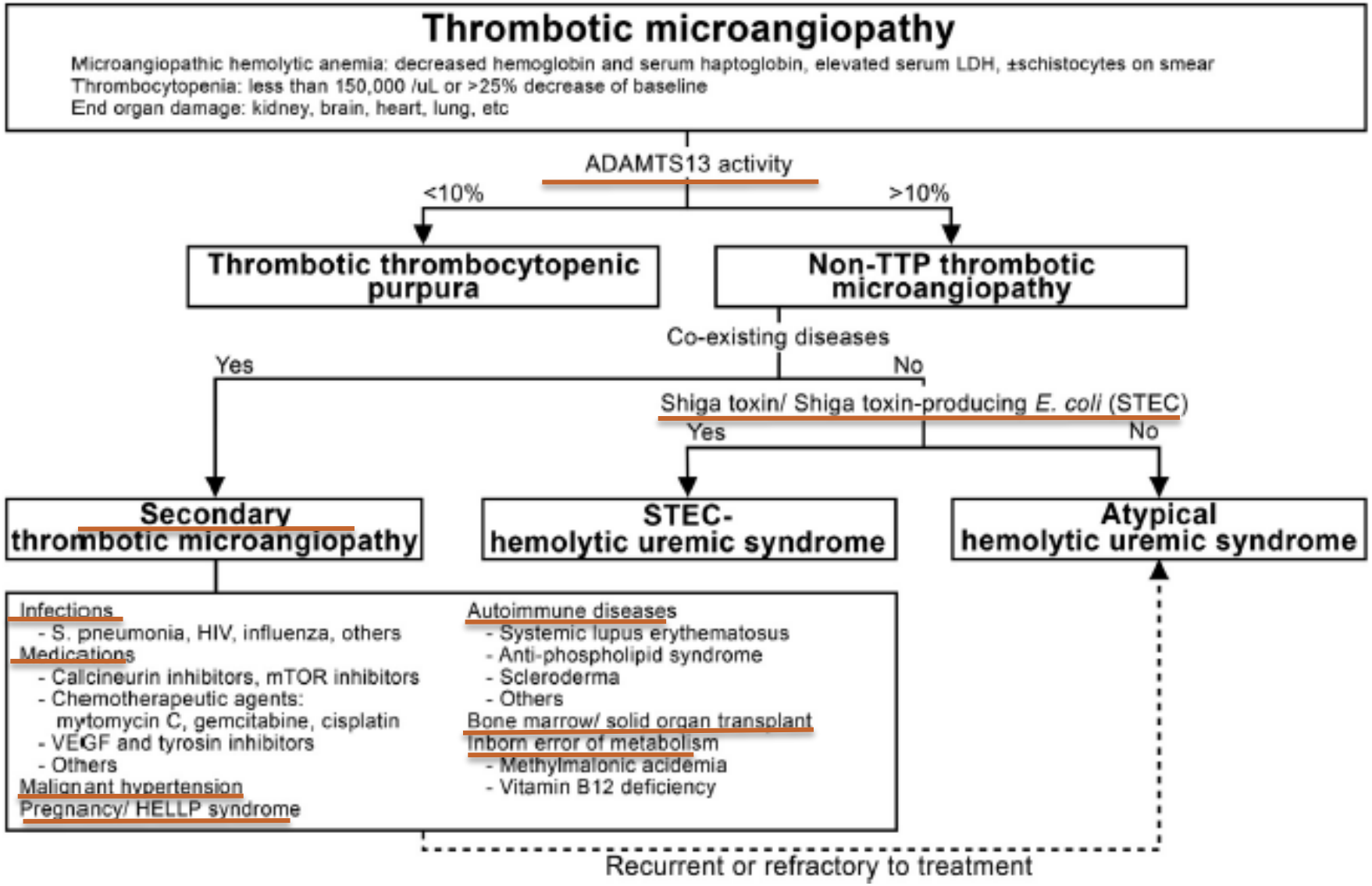
Clinical Features and Diagnosis

- Vary widely, may present as nausea, vomiting, abdominal pain,diarrhoea, headache, altered mental status,hypertension
- Renal impairment almost always seen and often more severe than TTP
- Genetic testing and FH Ab should be conducted in all patients- important for risk of relapse and recurrence and duration of treatment.
- But NOT USED TO MAKE A DIAGNOSIS of CM-TMA

Burwick RM et al. Hypertension. 2021
Java A et al. J Rheumatol. 2023



Yerigeri et al. Journal of Multidisciplinary Healthcare. 2023



Tseng et al. aHUS: Consensus of diagnosis and treatment in Taiwan. JFMA. 2023

Treatment and Prognosis

- C_5 inhibition current mainstray of treatment
  - Eculizumab- humanized monoclonal antibody to C_5 which blocks activation of terminal pathway and prevents MAC formation
  - Ravulizumab- newer longer acting C_5 inhibitor

- Prior to the approval of C_5 inhibitors, PLEX was mainstay although overall efficacy was poor

  Rationale:

  - Reduce quantity of mutant protein and deliver functionally normal protein by plasma infusion
  - Removing and decreasing titers of aFH Ab, and replenishing CF like FH and FI
  - Plasma therapies still remain initial treatment of choice in countries where complement inhibitors are not available, or cost precludes its use

Fakhouri et al. Blood. 2020
Huerta A et al. Kidney Int. 2018
Kelly RJ et al. N Engl J Med. 2015

- No established best treatment for aHUS with FH Ab, but most efficient is PEX combined with immunosuppressant

- Immunosuppressants (prednisone, cyclophosphamide, azathioprine, mycophenolate mofetil, and rituximab) inhibit formation of Ab- also used as maintenance therapy
- Close monitoring of Ab titers for 3-6 months due to risk of relapse following minor infection
- Another reason for relapse is cessation of PEX
- Eculizumab can be considered as additional therapy- provides better renal recovery, and in cases of severe extrarenal manifestations (serious cardiac or brain injury)

- ...but none of these therapies by themselves have been effective in removing Ab

- Optimal duration of anticomplement therapy also remains unclear

- KDIGO Consensus Conference 2015- experts recommendation on case-by-case basis, at least 6 to 12 months of treatment and at least 3 months of stabilization of kidney function

- Close monitoring, and prompt reinitiation of treatment in relpase is crutial

Reina et al. Front Immunol. 2022
Schwartz J et al. J Clin Apher. 2016

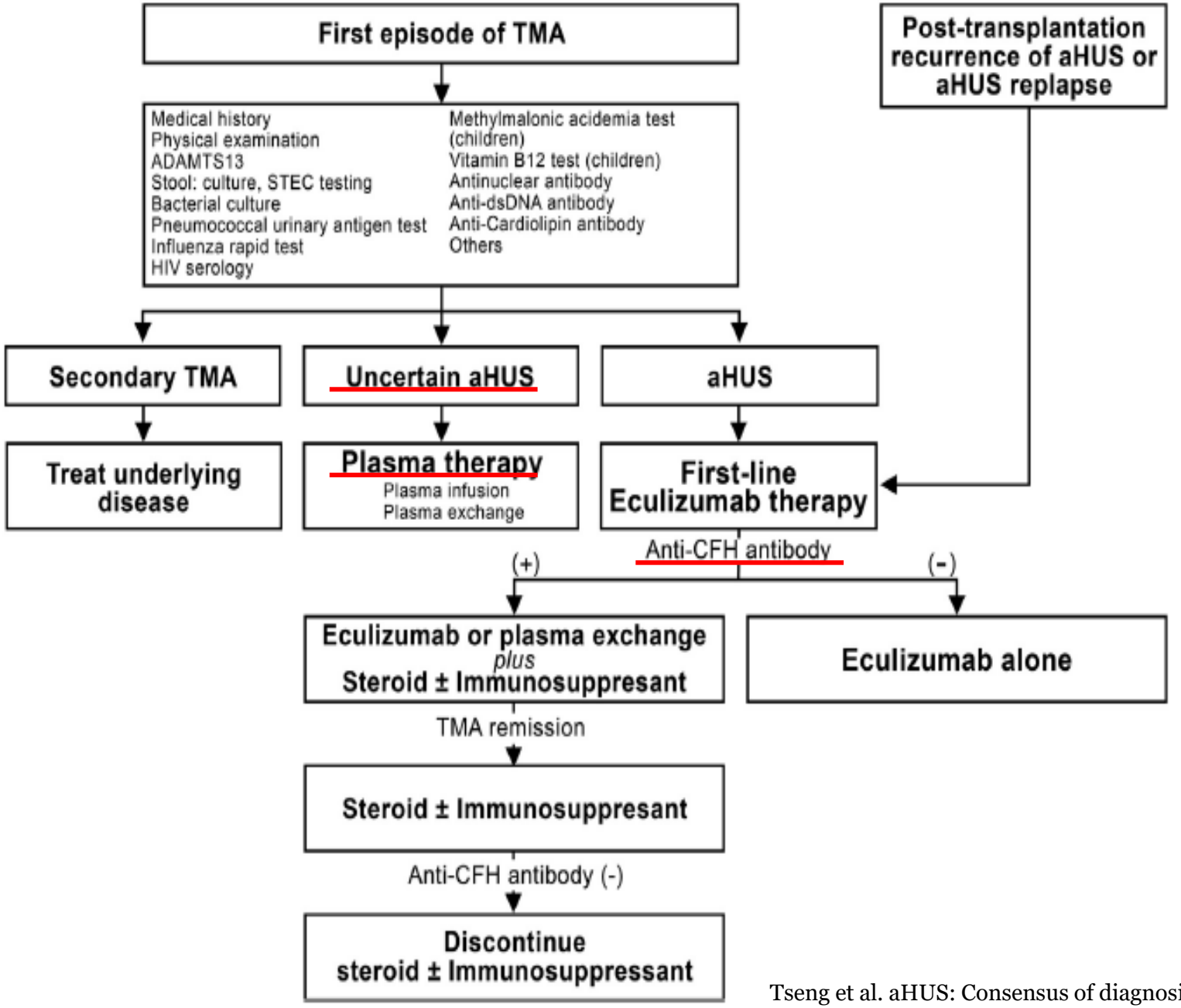
- Promptly initiate treatment while awaiting diagnosis confirmation
- Prognosis of TTP: before PLEX survival was 10%, now in first episode is 80% to 90%
- iTTP treatment: Daily PLEX (1 to 1.5 plasma volume using FFP)
- Continue for minimum 2 days after normalization of neurological status, PLT and LDH, rising Hgb, taper rather than stopping abruptly to minimize risk of relapse
  - PLEX is effectively removing autoAb and VWF multimers while replacing functional ADAMTS13 and FFP components
- ….and CS (oral prednisone 1 mg/kg/day).

Little et al. Kidney Int Rep. 2017
Fakhouri F et al. Blood. 2020

Treatment- cTTP

- Administration of FFP (replaces deficient ADAMTS13)
- In severe cases PLEX may remove VWF multimers
- New therapeutic arsenal- recombinant ADAMTS13

Fakhouri F et al. Blood. 2020



Tseng et al. aHUS: Consensus of diagnosis and treatment in Taiwan. JFMA. 2023

ASFA 2023

TABLE 1 (Continued)

Disease/condition	Indication	Procedure	Category	Grade	Page
		TPE	III	2C	
Thrombocytosis	Symptomatic	Thrombocytapheresis	II	2C	229
	Prophylactic or secondary	Thrombocytapheresis	III	2C	
Thrombotic microangiopathy, coagulation mediated	*THBD, DGKE*, and *PLG* mutations	TPE	III	2C	231
Thrombotic microangiopathy, complement mediated	Factor H autoantibody	TPE	I	2C	233
	Complement factor gene mutations	TPE	III	2C	
Thrombotic microangiopathy, drug induced	Ticlopidine	TPE	I	2B	235
	Clopidogrel	TPE	III	2B	
	Gemcitabine	TPE	IV	2C	
	Quinine	TPE	IV	2C	
Thrombotic microangiopathy, infection associated	STEC-HUS, severe	TPE/IA	III	2C	237
	pHUS	TPE	III	2C	
Thrombotic microangiopathy, pregnancy associated	Pregnancy associated, severe	TPE	III	2C	239
	Extremely preterm preeclampsia, severe[a]	TPE/LA	III	2C	
Thrombotic microangiopathy, thrombotic thrombocytopenic purpura		TPE	I	1A	241
Thrombotic microangiopathy, transplantation associated		TPE	III	2C	243

THROMBOTIC MICROANGIOPATHY, COMPLEMENT MEDIATED

Incidence: 0.2 to 1.9 per million (all ages)

Indication	Procedure		Category	Grade
Factor H autoantibody	TPE		I	2C
Complement factor gene mutations	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Factor H autoantibody	0	0	8 (217)†	NA
Complement factor gene mutations*	0	1 (31)	25 (406)†	NA

*Studies include some patients who were not tested or were tested and found negative for complement factor gene mutations; †one CS (Khandelwal, 2019) contributed Factor H autoantibody ($N = 74$) and other patients included under complement factor gene mutations ($N = 35$).

- Management: TPE and/or eculizumab with immunosuppression

TPE prescription:

- Plasma volume: 1-1.5 EPV
- Frequency: Daily
- Replacement fluid: Frozen plasma or frozen plasma/albumin
- Duration: Until adequate clinical response or Ab titer reduced to less than clinical threshold (similar to iTTP)

- TPE/PLEX removes aberrant complement regulatory proteins, abnormally activated complement cascade components, and aFH Ab
- Does not address underlying genetic abnormality, and patients may not respond
- TPE is used as initial empiric treatment until other causes of TMA excluded, mutations confirmed,and to control crisis at presentation; subsequent therapy should consist of anticomplement therapy
- There is no "usual" course of TPE for these disorders, with therapy determined by patient response
- Suggested to continue TPE if there is ongoing organ response and discontinued, with initiation of eculizumab therapy, if patients are refractory to (failure to respond to TPE within 3 to 5 days) or dependent on TPE

Winters. Hemathology. 2017

The Turkish Journal of Pediatrics 2021; 63: 986-993
https://doi.org/10.24953/turkjped.2021.06.006

Original Article

Could plasma based therapies still be considered in selected cases with atypical hemolytic uremic syndrome?

Sare Gülfem Özlü[1], Bora Gülhan[2], Özlem Aydoğ[3], Emine Atayar[4], Ali Delibaş[5], Gönül Parmaksız[6], Elif Bahat Özdoğan[7], Elif Çomak[8], Mehmet Taşdemir[9], Banu Acar[10], Zeynep Birsin Özçakar[11], Rezan Topaloğlu[2], Oğuz Söylemezoğlu[12], Fatih Özaltın[2,4]

ABSTRACT

Background. Atypical hemolytic uremic syndrome (aHUS) occurs due to defective regulation of the alternative complement pathway (ACP) on vascular endothelial cells. Plasma based therapy (PT) was the mainstay of the treatment for aHUS for many years until the introduction of therapies targeting blockage of the complement system. The aim of this study was to evaluate patients with aHUS who had been treated with plasma based therapies alone.

Methods. The outcomes of seven genetically confirmed aHUS patients (2 girls, 5 males) were evaluated by means of clinical presentation, response to plasma therapy, course of the disease during the follow-up period and last status.

Results. The median age of the patients at admission was 6.7 years (IQR 0.7-7.8). Three patients received plasma exchange therapy and the other four patients were treated with plasma infusions. One patient was lost to follow-up after one year; the median duration of follow-up for other patients was 3.7 years (IQR 2.7-6.5). During the follow up, two patients from our historical records when complement blocking therapies had not been in clinical use yet in Turkey, underwent kidney transplantation. One transplant patient experienced an acute rejection episode without graft loss. The remaining five patients had a glomerular filtration rate of more than 90 ml/min./1.73 m^2 at the last visit.

Conclusion. Although we had a relatively small patient population, our findings indicate that PT might still be considered in selected patients particularly in countries where complement blocking therapies are difficult to reach due to their unavailability or costs that are not covered by the health care systems.

CFHR1-3 deletion with anti-CFH Ab (n=1)- ESRD
CFH (n=1)- ESRD
CFB (n=2)
C3 (n=1)
CD46 (MCP) (n=1),
DGKE variation (n=1)

- Better response to plasma treatment was observed in children than in adults
- Rationale behind using TPE instead of infusion is that it also removes mutant circulating molecules and aFH Ab and allows administration of higher volumes of plasma without risk of fluid overload
- Plasma therapy could be beneficial in patients with mutations in **circulating** complement regulators
- In *MCP* mutations, plasma therapy did not affect outcome, for MCP is not circulating protein but this again decided on individual basis
- Response to TPE varies depending on mutation
- In *CFH* mutations, complete or partial remission was achieved in majority of plasma-treated episodes with less favorable results in *CFI* mutations
- Better responses occur among those with FH, C3, and aFH Ab (55%-80%) compared with those with FI mutations (25%)

Noris et al. Clin J Am Soc Nephrol. 2010
Bresin et al. AJKD. 2013

- Some reports show that most patients carrying single-gene mutations undergo remission on plasma treatment
- Others show same in combined-mutated patients
- Careful genetic characterization, allowing prediction of disease phenotype and risk of post-transplant recurrences, could help selection of patients who may need and benefit most from anticomplement therapy
- Could be useful to exclude from anticomplement therapy patients with single MCP mutations who are reported to have good post-transplant outcome or patients with anti-CFH antibodies who may benefit from plasma exchange, steroids, or immunosuppression

Bresin et al. AJKD. 2013

Pediatr Nephrol (2008) 23:1517–1521
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ORIGINAL ARTICLE

Plasma therapy in atypical haemolytic uremic syndrome: lessons from a family with a factor H mutation

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Abstract Whilst randomised control trials are undoubtedly the best way to demonstrate whether plasma exchange or infusion alone is the best first-line treatment for patients with atypical haemolytic uremic syndrome (aHUS), individual case reports can provide valuable information. To that effect, we have had the unique opportunity to follow over a 10-year period three sisters with aHUS associated with a factor H mutation (*CFH*). Two of the sisters are monozygotic twins. A similar natural evolution and response to treatment would be expected for the three patients, as they all presented with the same at-risk polymorphisms for *CFH* and *CD46* and no identifiable mutation in either *CD46* or *CFI*. Our report of different modalities of treatment of the initial episode and of three transplantations and relapses in the transplant in two of them, strongly suggest that intensive plasma exchange, both acutely and prophylactically, can maintain the long-term function of both native kidneys and allografts. In our experience, the success of plasma therapy is dependent on the use of plasma exchange as opposed to plasma infusion alone, the prolongation of daily plasma exchange after normalisation of haematological parameters followed by prophylactic plasma exchange, the use of prophylactic plasma exchange prior to transplantation and the use of prophylactic plasma exchange at least once a week posttransplant with immediate intensification of treatment if there are any signs of recurrence.

Patients	Older sister	Twin 1	Twin 2
Native kidneys			
Age (years) at presentation	3	4	4.5
PE (40 ml/kg/session)	No	10 daily sessions initially	21 daily sessions initially
Pl Cr (µmol/l) response to initial PE		166→ 137	132→ 61
Pl (10 ml/kg)	No	3 courses of 5 Pl	No
Prophylactic PE 1×2w	No	No	Yes
Relapses	Immediate ESRF	3 relapses of haemolysis and thrombopenia	2 after 3 and 19 months, respectively
Outcome	Immediate ESRF	Progressive degradation of renal function. ESRF after 4 months	Pl Cr 66 µmol/l after 6 years, no urinary abnormality
Tx 1	Cadaver	Cadaver	No
Prophylactic PE 1/w	No plasma therapy	Yes after initially prior Tx and daily during 7 days post-Tx	
Immunosuppressive therapy	ATG, Pred, AZA, CsA	Pred, MMF, CsA (low doses), Basiliximab	
Relapses	2 days after Tx no plasma therapy	2 relapses concomitant to CMV primo-infection and reactivation; successful treatment with daily PE and ganciclovir	
Outcome	Transplantectomy	P2 Cr 127 µmol/l 5 y after Tx	
Tx2	Cadaver	No	No
Prophylactic PE **1/w**	During the first 2 month, after initially prior Tx and daily during 7 days post-Tx		
Prophylactic PE **1/2w**	Initiated 2 months post-Tx		
Immunosuppressive therapy	Pred, MMF, CsA(low dosis), Basiliximab		
Relapse	Occurred when PE frequency shift to 1/2w;		
Outcome	Immediate post-Tx function (Pl Cr 80 µmol/l until day 60). Transplantectomy at day 75 related to late initiation of daily PE		

Therapeutic Apheresis and Dialysis

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Atypical Hemolytic Uremic Syndrome: A Meta-Analysis of Case Reports Confirms the Prevalence of Genetic Mutations and the Shift of Treatment Regimens

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- Despite limitations associated with metaanalysis of case studies, study provides enough aHUS cases to draw conclusions cautiously
- Reports of aHUS cases and use of eculizumab significantly increased during last 5-year period which may be due to its approval by FDA and EMA in 2011 or may reflect growing interest in aHUS resulting in increased rates of publication
- PLEX remained most used initial treatment modality for aHUS as majority of analyzed patients and most CFH Ab positive cases underwent PLEX
- There was a decrease in CFH, CFI and MCP mutations in last 5-year period compared to precedent for unknown reasons
- Although significant reduction in mortality rate was observed with eculizumab, there were no differences in time to resolution of symptoms or serum creatinine or platelet normalization with the eculizumab or plasma therapy
- aHUS is acute and life-threatening, so PLEX may be initiated before confirmed diagnosis and in patients positive for CFH Ab

Complications of PLEX

Table 7. Complications Associated With TPE

Complication	Mechanism	Frequency
Access-related		
Peripheral access	Hematomas, nerve damage, sclerosis of veins/arteries	1.48%
CVC	Thrombosis, infections, pneumothorax, arterial puncture, air embolism	0.11%-0.36% (more complications in subclavian [60%] vs jugular [20%] CVCs)
Ports	Early: pneumothorax, hematomas, arrhythmia, arterial puncture; late: thrombosis, port-pocket infection, pinch-off syndrome	18%
AVF/AVG	Thrombosis	12%-20%
	Inadequate maturation	60%
Anticoagulation-related		
Hypomagnesemia	Citrate chelation	NA
Thrombocytopenia	Heparin-induced thrombocytopenia	1%-5% (not specific to TPE)
Procedure-related		
Anemia	Hematocrit may decrease 10% due to intravascular expansion with hyperoncotic fluids; hemolysis if hypo-oncotic priming solutions used	NA
Hypotension, dyspnea, chest pain	Complement-mediated membrane bioincompatibility; ethylene oxide hypersensitivity	0.4%-15%
Thrombocytopenia	Loss of platelets in the discarded plasma, circuit clotting, or dilutional effect by replacement fluid	NA
Vitamin deficiencies	Depletion of protein-bound vitamins (A, B_6, B_{12}, C, and E and β-carotene) of 24%-48% with rebound to pretreatment levels within 24 h	NA
Replacement fluid–related		
Anaphylactoid reactions	Transfusion of IgA in donor plasma to patients with selective IgA deficiency; contamination with bacteria, endotoxins, pyrogens; presence of prekallikrein activator and bradykinin (ACEI); antibodies to polymerized albumin (rare)	0.02%-0.07%
Coagulopathy	Depletion of coagulation factors and its inhibitors related to albumin replacement alone (Table 4)	0.06%-0.14% for thrombosis, 0.06% for bleeding
Electrolyte/acid base abnormalities	Hypokalemia (albumin), hypocalcemia (frozen plasma), hypomagnesemia (frozen plasma), metabolic alkalosis (frozen plasma)	9%-19.6% for hypocalcemia, 0.03% for alkalosis
Infection	Hypogammaglobulinemia (albumin), viral transmission (frozen plasma)	NA
Transfusion-related lung injury	Transfusion of donor antibodies (frozen plasma)	NA
Hypervolemia	Administration of replacement fluid	NA

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter; IgA, immunoglobulin A; NA, not applicable; TPE, therapeutic plasma exchange.

Cervantes et al. AJKD. 2023

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RESEARCH ARTICLE

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Membrane-filtration based plasma exchanges for atypical hemolytic uremic syndrome: Audit of efficacy and safety

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ABSTRACT

Background: While complement blockade with eculizumab is recommended as first-line therapy of atypical hemolytic uremic syndrome (aHUS), plasma exchanges (PEX) remain the chief option for anti-factor H (FH) antibody associated disease and when access to eculizumab is limited.

Methods: We reviewed adverse events (AEs) and adverse outcomes (eGFR <30 mL/min/1.73 m^2 or death), in all patients with aHUS managed with membrane-filtration based PEX at one tertiary care center over 5.5 years.

Results: During January 2013 to June 2018, 109 patients with aHUS (74 with anti-bodies to FH), aged median (range) 7.6 (0.5-18) year weighing 22.1 (6-90) kg, underwent 2024 sessions of PEX. AE, in 12.1% patients, were usually self-limiting and included chills (5.5%), vomiting/abdominal pain (3.3%), hypotension (1.6%), urticaria (1.5%), seizures (0.2%), hypocalcemia (0.2%), and hemorrhage (0.1%); plasma hypersensitivity and severe reactions were rare. Rate of catheter-related infections was 1.45/1000 catheter-days. Filter reuse (OR 1.69; 95% CI 1.26-2.26; $P < .001$) and >20 sessions of PEX/patient (OR 1.99; 95% CI 1.27-3.10; $P = .002$) were independently associated with adverse events; infusion of IV calcium gluco-nate during PEX was protective (OR 0.26; 95% CI 0.16-0.43; $P < .001$). Hemato-logical remission was achieved in 96.3% patients after 6 (5-8) PEX sessions; 80.8% and 89.6% patients were dialysis independent by one and 3 months, respectively.

Conclusions: PEX is safe and associated with satisfactory short-term outcomes in chil-dren with aHUS. Prolonged PEX and filter-reuse are associated with complications.

KEYWORDS

central venous catheter, clinical audit, complement factor H, plasmapheresis

PEX remain mainstray of therapy for aHUS in many developing regions including India for eculizumab is not available and is prohibitively expensive

It is not marketed in large parts of Asia and Africa, leading nephrologists to rely on plasma therapy

More than half of patients had anti-FH Ab associated aHUS

Combining PEX with immunosuppression is useful in anti-FH associated disease

Trend towards better outcomes in patients with Ab, but overall outcomes were comparable between patients with and without anti-FH aHUS

Potential reasons for better outcomes in anti-FH negative patients as compared to previous reports are exclusive use of PEX instead of plasma infusions and timely initiation of PEX

PEX is safe and effective in inducing hematological remission and resolving renal dysfunction

In absence of access to eculizumab, PEX remains a reasonable alternative in patients with aHUS

Rates of procedure and access related AE are low, even in young children

CONCLUSIONS

- cTMA/aHUS is organ and life-threatening condition for which prompt initiation of curative, but also empiric and supportive therapy is of great importance
- There is no diagnostic test for aHUS and complement assays and results of gentic tests are not required for diagnosis at acute phase
- PLEX is important initial therapy if high clinical suspition of aHUS and in countries where eculizumab is difficult to attain or resources are limited, it is reasonable alternative
- Although terminal complement inhibition is effective and suggested as first line therapy in recent years, main limitations is its cost and unavailability in some countries and it also brings significant risks that could be life-threatening including severe infections and allergic reactions
- Alternative approaches, including PLEX, are certainly needed and research on these approaches, varied responsiveness to PLEX, dialysis, and eculizumab may guide future directed therapy
- Short- and long-term management of patients with aHUS should be tailored individually considering the patient's clinical course, underlying genetic abnormality and current conditions of healthcare systems of countries
- Extensive research is undertaken on genetic studies, gene editing, and biosimilar drugs. Research should also focus on quicker and more readily available diagnostic modalities that will ensure timely management and rehabilitation