TMA treatment

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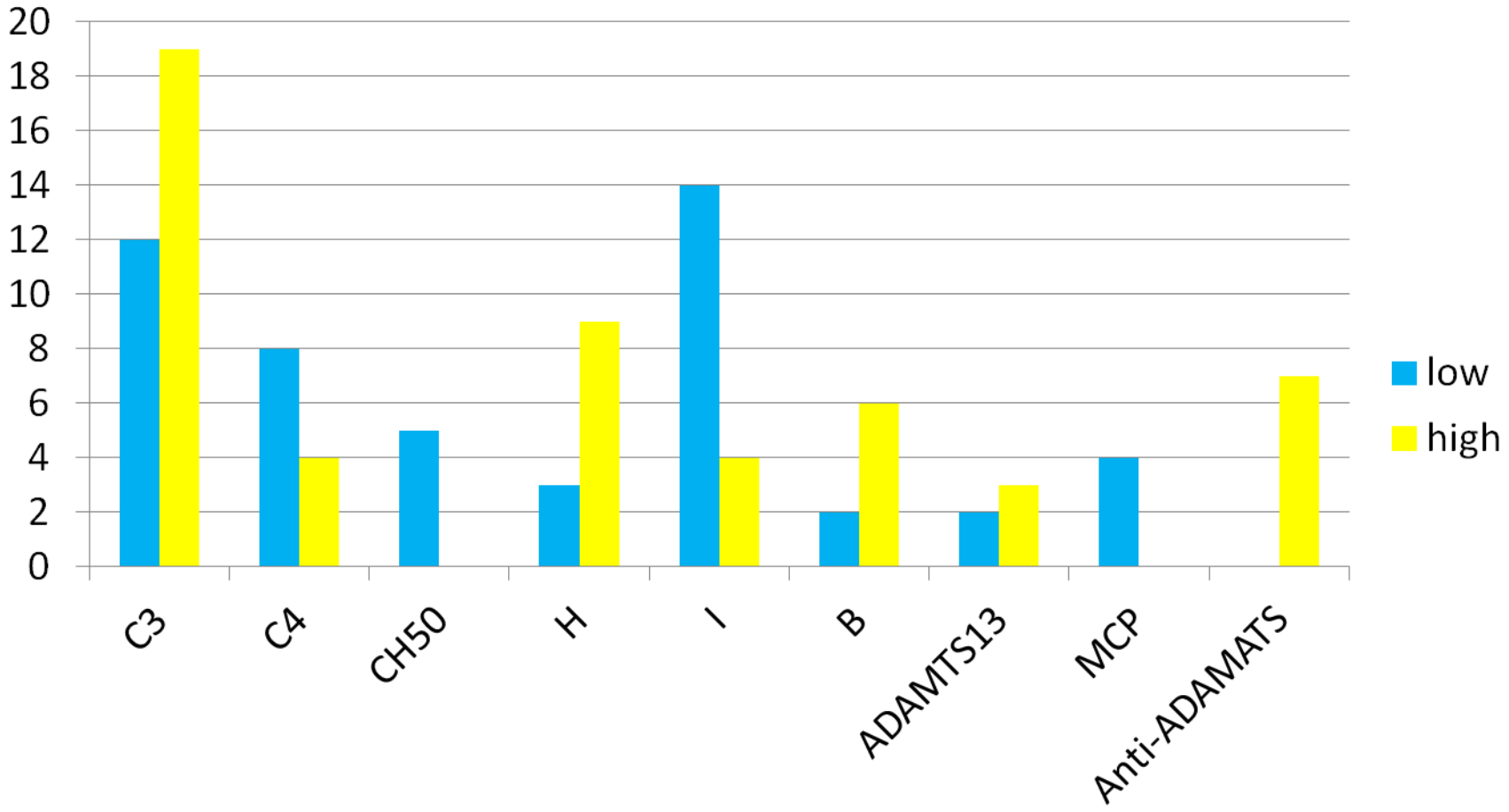
THE PREVALENCE AND INCIDENCE OF aHUS IN IRAN

- SR-MA-January 1985 and January 2016
- 25 articles and two abstract of congress containing 6728 patients
- The incidence aHUS was
  - 34.57 pmp
  - 0.88 pmp/ year of children <15 years old.
- The mean annual incidence rate
  - 0.12 <2000
  - 0.74 > 2010
  - Acute kidney injury (13%)
  - CKD , ESRD -5.48%(95%CI: 3.5–7.9))

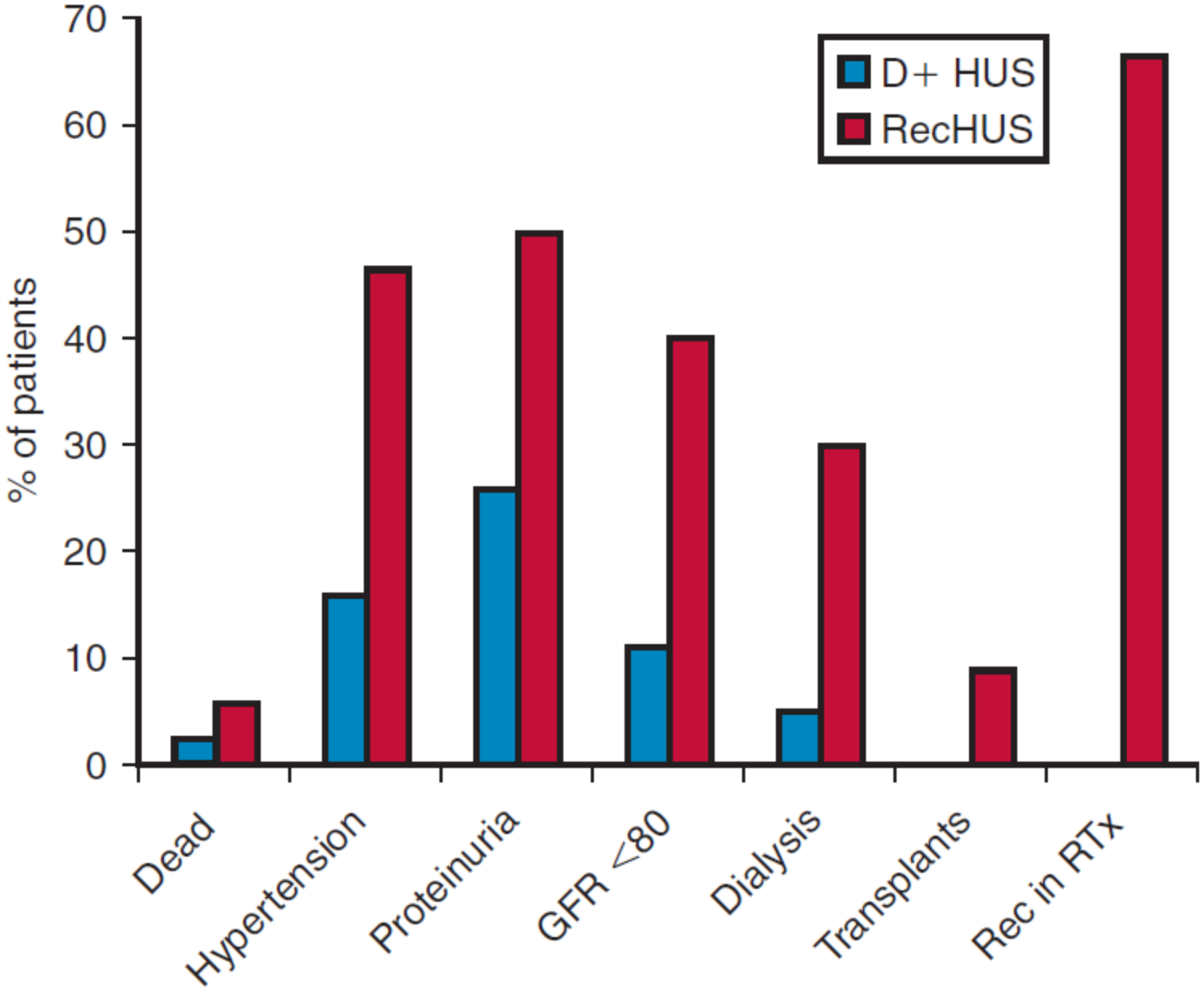
Pediatr Nephrol (2017) 32:1643–1834

Complement level in HUS(N=31)



Hooman et al. JPN 2018

Clinical outcome of Patients with Recurrent HUS after one year



Initial Treatment

- Supportive
  - Correct anemia (Hb<6 g/dl) to target 8-9 g/dl
  - Fluid and electrolyte correction
  - Dialysis – uremia or anuria
  - Avoid platelet infusion unless hemorrhage
  - Seizure >> anticonvulsant
  - HTN>> CCB>> if chronic (RASB)

Infectious associate HUS

- S. pneumonia
  - Appropriate antibiotic
  - Avoid FFP , unwashed RBC, Platele
- STEC- HUS
  - Supportive
  - Avoid antibiotic
  - Ecluzimab for brain, cardiac, multivisceral involvement

STEC-HUS

Pre-complement inhibitors era

Children

	USA 1997-2012[77] O157 predominant	Austria/Germany 1997-2002[76] O157 predominant
	Supportive treatment N=770	Supportive treatment ± PE N=619
At baseline		
Dialysis requirement	57%	65%
Neurological complications	3%	29%
At discharge		
Dialysis requirement	7.3%	0.1%
Death	2.9%	1.4%
Mean SCr (µmol/L)		

Complement inhibitors era

Children

	O104 outbreak, Germany 2011[82] Retrospective analysis
	Eculizumab (n=13) vs supportive treatment ± PE (n=77)[a]
At baseline	
Dialysis requirement	71%
Neurological complications	77% vs 17%
At 4 months	
Dialysis requirement	1.1%**
Death	1.1%
Mean SCr (µmol/L)	

Adults

	O104 outbreak, Germany 2011[84] Retrospective analysis	O104 outbreak, Germany 2011[85] Retrospective analysis
	PE/eculizumab (n=193) vs PE (n=241) and BSC (n=57)[b]	PE/eculizumab (n=67) vs severity-matched PE controls (n=65)[c]
At baseline		
Dialysis requirement	75% vs 52%** and 21%**	76% vs 82%[#]
Neurological complications	64% vs 39%** and 25%**	73% vs 66%[#]
At discharge		
Dialysis requirement	4.7% vs 3.7%[#] and 0%[#]	0% vs 0%
Death	2.6% vs 3.7%[#] and 10.5%[#]	5% vs 8%[#]
Mean SCr (µmol/L)	124 vs 106[#] and 97**	154 vs 206[#]

Predictors

In-hospital death	Long-term renal sequels
Age > 60 y	Children
Children	Ht ≥ 20-23%
Ht ≥ 20-23%	WBC >20000/µL
WBC > 25400/µL	Dialysis duration

5-year outcome

Full renal recovery, 70%
Hypertension, 9%
Proteinuria, 19%
CKD stage 2, 9%
ESRD, 1.4%
Neurological sequelae, 4%

3-year outcome[83]

Full renal recovery, 55%
Hypertension, 36% vs 16%[#]
Proteinuria 30% vs 27%[#]
CKD stage 3, 1.3%
ESRD, 2.7%
Neurological sequelae, 1.3%

Uncertain benefit of eculizumab for short and long-term outcome. Eculizumab efficacy assessed in 2 ongoing prospective randomized trials in children

Management

Prevention/correction of dehydratation
Transfusion of packed RBC
Dialysis if required
Detection and treatment of extrarenal complications (neurological, cardiac, intestinal/pancreatic)

Plasma infusions
Heparin, urokinase, dipyridamol
Shigatoxin synthetic receptor (p.o.)
→ No proven benefit in prospective randomized trials[81]

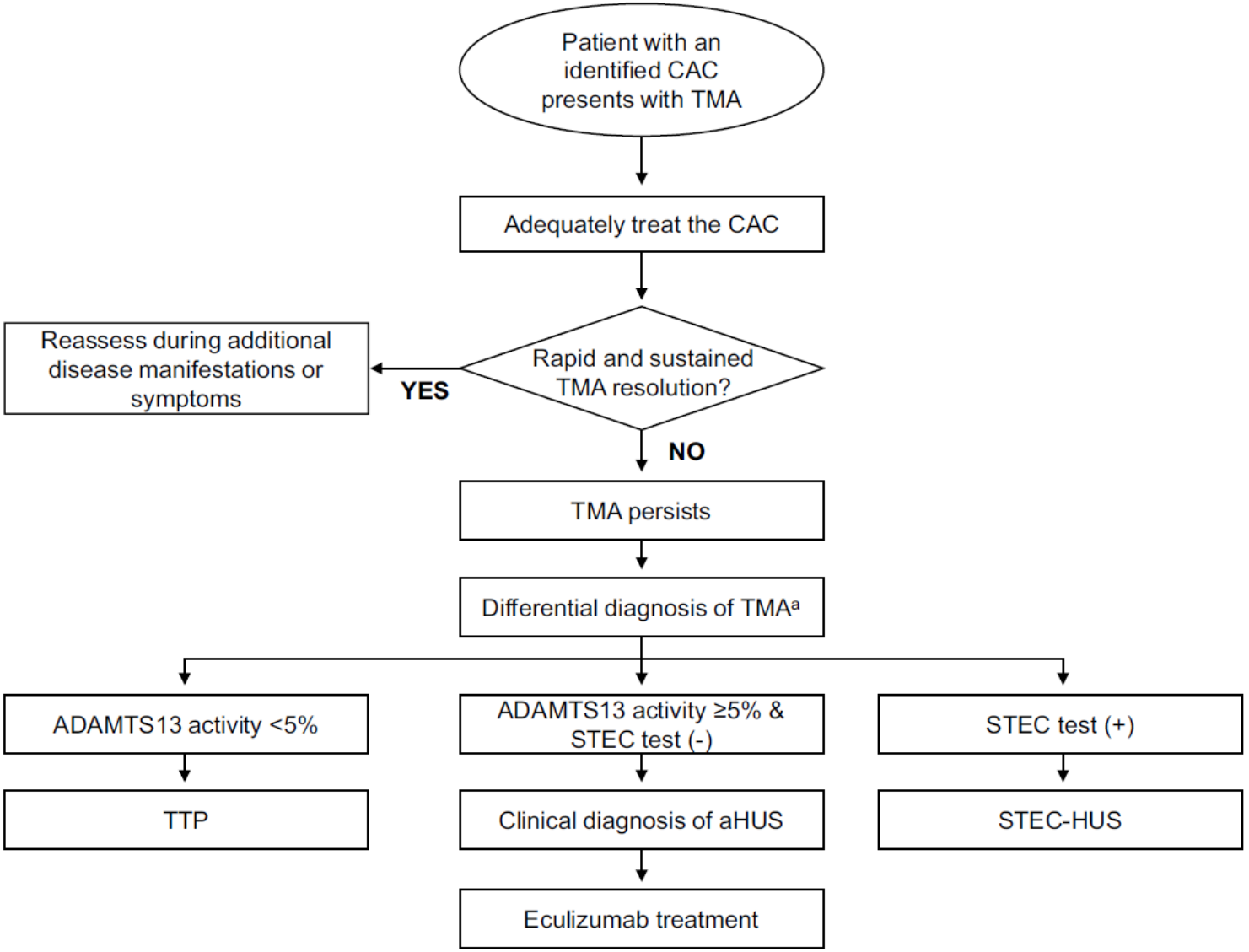
Plasma exchanges
with or without glucocorticoids
→ No benefit in children[76] and adults (case-control study)[85]

Antibiotics
→ Adults treated with antibiotics during the O104 outbreak had fewer seizures and deaths and excreted E coli for shorter duration[87].
Azithromycin efficacy assessed in an ongoing prospective randomized trial in children

Eculizumab
→ Considered in patients with extra-renal complications.

Immunoadsorption

Complement Dysregulation

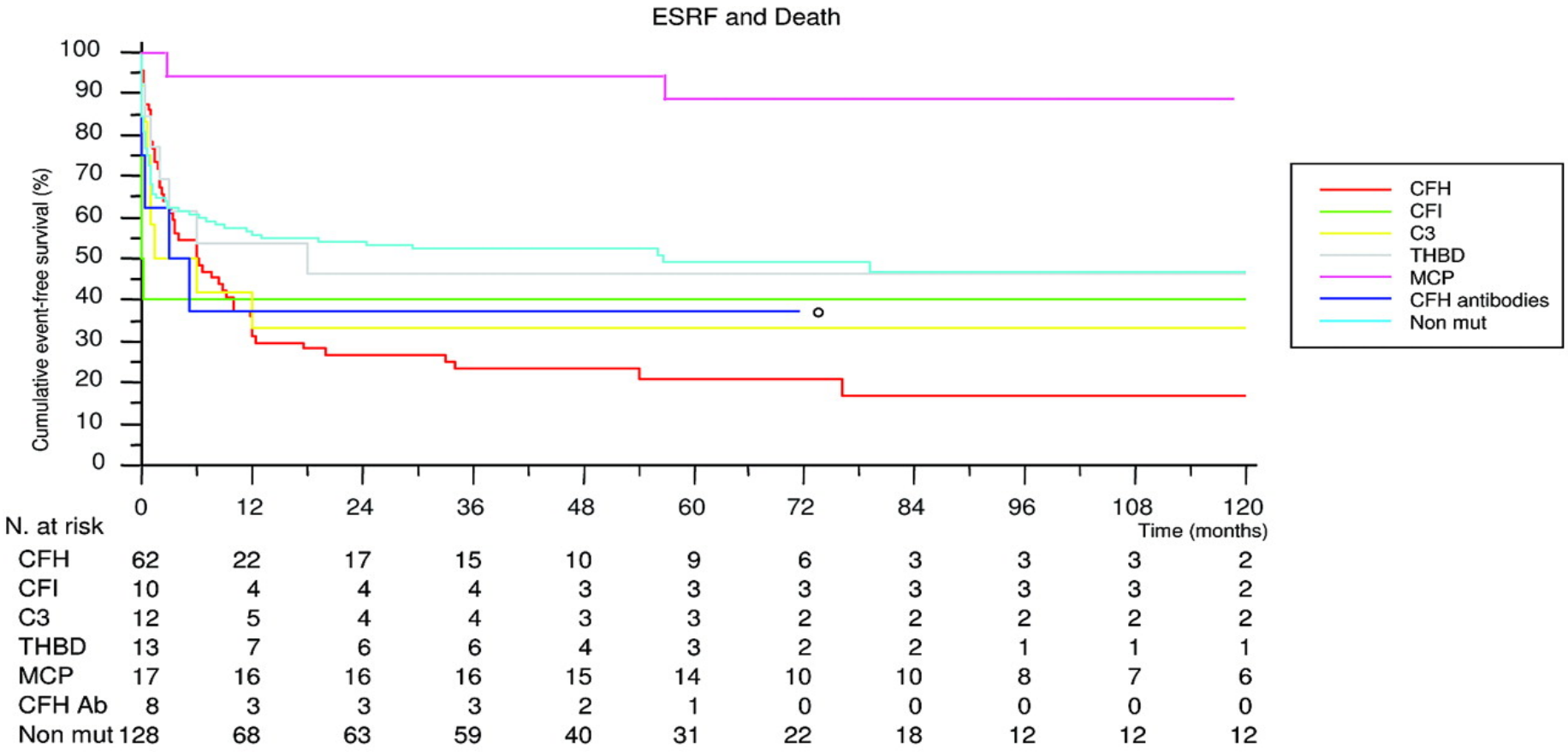


J Nephrol (2017) 30:347–362

Genotype – phenotype correlation

Protein	%	Response to PE (*Remission*)	Long-term outcome (*Death or ESRD*)	Outcome after kidney tx (*Recurrence*)
Factor H	20-30%	60%	70-80%	80-90%
Factor I	4-10%	30-40%	60-70%	70-80%
C3	5-10%	40-50%	60%	40-50%
Factor B	1-2%	30%	70%	Recurrence in 1 case
MCP	10-15%	Not indicated	<20%	15-20%
Thrombomodulin	5%	60%	60%	Recurrence in 1 case
Anti-FH-Ab	6-10%	70-80% (PE + IS)	30-40% ESRD	20%

Norris NEJM 2009



Comparison	HR	95% C.I.	P value
CFH vs MCP	13.55	3.29-57.79	<0.0001
CFH vs non mut	1.73	1.19-2.51	0.0032
CFI vs MCP	7.83	1.55-39.54	0.0028
C3 vs MCP	9.62	2.02-45.75	0.0006
THBD vs MCP	6.88	1.41-33.75	0.0066
CFH Ab vs MCP	8.49	1.61-44.69	0.0028
Non mut vs MCP	6.08	1.49-24.76	0.0037

aHUS : PLASMATHERAPY (1)

In practice : what should be done at admission ?

« Guideline for initial therapy », European Pediatric Study Group for HUS

in press, Pediatr Nephrol 2008

(1) When to start ?

- as soon as possible (within 24 h)
  as soon as the patient's condition allows it (BP, volemia, hydroelectrolyte equilibrium, anemia…)

- question : even if serum creatinine not elevated ?
  yes, because :
  * approximately 50 % of HUS with CFH mutation go to ESRD at the 1st episode

  * delay in treatment initiation can be deleterious in HUS with anti-CFH antibodies

(2)

(2) Which volume ?

- Exchange 1.5 plasma volume (60-75 ml/kg) with FFP for restitution
- If PE is impossible, infuse FFP 10-20 ml/kg (if BP and cardiac function OK)

(3) Which frequency during the first month ?

- daily x 5 days
- 5/week x 2 weeks
- 3/week x 2 weeks

(4) What are the situations which allow not to do PE or to stop early ?

- MCP mutation (PE only during relapses ?)

(5) Which frequency after the 1st month ?

empirical : try to find the threshold dose (PE or FFP infusion) and interval for each individual patient

Table 5. Outcomes after plasma treatment in aHUS patients with mutations in *CFH, CFI, C3, THBD, MCP*, or CFH autoantibodies and in patients without mutations

Mutation	CFH	CFI	C3	THBD	MCP	CFH Antibodies	None
Plasma treated episodes	**90** (52 patients)	**8** (7 patients)	**14** (10 patients)	**8** (6 patients)	**29** (14 patients)	**12** (7 patients)	**103** (84 patients)
Remission	57 (63%)	2 (25%)[a]	8 (57%)[a]	7 (88%)	28 (97%)[b]	9 (75%)	71 (69%)[a]
Complete remission	5 (5%)	1 (12.5%)[a]	6 (43%)[a,b]	5 (62%)[b]	26 (90%)[b]	3 (25%)	30 (29%)[a,b]
Partial remission	52 (58%)	1 (12.5%)	2 (14%)[b]	2 (25%)	2 (7%)[b]	6 (50%)[a]	41 (40%)[a]
ESRF–death	33 (37%)	6 (75%)[a]	6 (43%)[a]	1 (13%)	1 (3%)[b]	3 (25%)	32 (31%)[a]
ESRF	25 (28%)	6 (75%)[a]	6 (43%)[a]	—	1 (3%)	3 (25%)	31 (30%)
Death	8 (9%)	—	—	1 (13%)	—	—	1 (1%)

Complete remission is defined as normalization of both hematologic parameters and of renal function (see Table 3). Partial remission is defined as normalization of hematologic parameters with renal sequelae (see Table 3). In this table, we included only the episodes for which information about plasma treatment was available. CFH group includes two patients with CFH mutations and CFH autoantibodies and three patients with the *CFH/CFHR-1* hybrid gene.

[a] $P < 0.0024$ after Bonferroni correction compared with the group with MCP mutations.

[b] $P < 0.0024$ after Bonferroni correction compared with the group with CFH mutations.

Ecluzimab

- first-line treatment?
  - ECU >> initiated within 24–48 h of onset or admission
  - PE (or PI if PE is not possible)
- Switch to ECU
  - PI/PE resistance
  - Subclinical hemolytic activity
  - Residual CKD
  - Extra-renal manifestation

- Dialyzed patients?
  - If on dialysis for 3-4 m>> maintained for 3-6 m before decision
  - Kidney biopsy

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

Patient body weight	Induction regimen	Maintenance regimen
40 kg and over	900 mg weekly x 4 doses	1,200 mg at week 5; then 1,200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

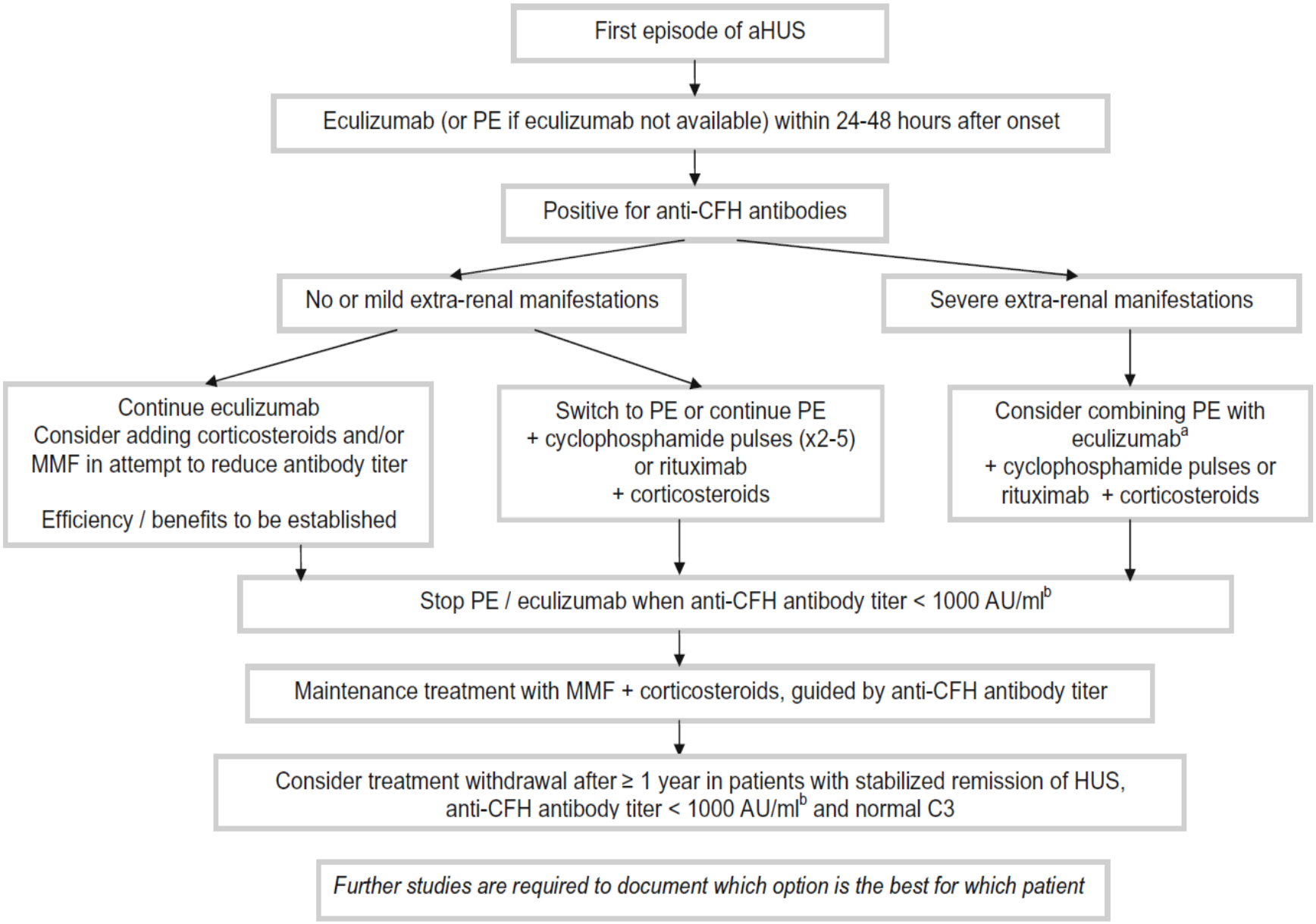
Efficacy ECU in aHUS

	Trial 1 [13, 77]		Trial 2 [13, 77]		Trial 3 [79]	Trial 4 [80]	
Median treatment duration[b]	26 weeks	2 years	26 weeks	2 years	26 weeks	26 weeks	1 year
Mean change in platelet count from baseline (G/L)	**73**	**75**	/	/	164	135	116.9
Normalization of platelet count[c] (% patients)	**82**	**88**	90	90	95	98	100
Hematologic normalization[c] (% patients)	**76**	**88**	**90**	**90**	82	88	97
TMA event-free status[c] (% patients)	88	88	**85**	**95**	/	90	90
Complete TMA response with preserved renal function[c] (% patients)	/	/	/	/	/	**73**	**80.5**
Complete TMA response with improved renal function[c] (% patients)	65	76	25	55	**64**	56	56
Mean increase in estimated glomerular filtration rate (eGFR) from baseline, ml/min/1.73 m^2 (95 % CI)	32 (14–49)	35 (17–53)	6 (3–9)	7 (0.8–14)	64 (50–79)	29 (SD24)	30 (SD27)
Patients on dialysis at data cut-off (%)		12		10	9	15	12
Death	0	0	0	1[d]	0	0	0

Pediatr Nephrol (2016) 31:15–39

Ecluzimub

- Check complement blockade? depends
- Interval? CH50<10%/ AHF<10%/ECU50-100
- Duration?
  - Few months after full recovery (MCP m/ CFI m)
    - >3-5 yrs old age
  - No withdrawal
    - Life-threatening initial presentation /relapse
      - Severe CNS manifestation
      - Myocardial failure
    - Not fully recover normal renal function



Pediatr Nephrol (2016) 31:15–39
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F. Fakhouri, C. Loirat / Seminars in Hematology 55 (2018) 150–158

ATYPICAL HUS

Pre-complement inhibitors era

Treatments

PE
PI

Prognosis

Risk of death[a]

F-up	Children	Adults
< 1y	5-11%	1-2%
3-5y	7-14%	2-4%

Risk of ESRD[a]

F-up	Children	Adults
1st episode	16%	46%
1y	29%	56%
3-5y	36-48%	64-67%

Risk of relapses[a]

F-up	Children	Adults
1st y	30%	30%
> 1st y	50%	20%

Complement inhibitors era

Prognosis

Prospective non controlled trials[b]

Risk of death[b]

F-up	Children	Adults
1y	0%	
2y		1%

Risk of ESRD[b]

F-up	Children	Adults
1y	9%	6-15%
2y		10-12%

Retrospective paired series[c] (adults)

Risk of ESRD[c]

F-up	3m	1y
PE	46%	63%
Eculizumab	17%	25%
P value	0.02	0.04

Prospective non controlled trials and retrospective series indicate that eculizumab is superior to PE

Risk of relapse after eculizumab discontinuation
High in patients with pathogenic variants in complement genes
Low in patients with no variant

Consider eculizumab discontinuation in children with complete renal remission and adults with stable kidney function

Diagnostic work-up of HUS
aHUS is an exclusion diagnosis

aHUS diagnosed

Adults — PE (3-7d) — Stop PE
Switch to eculizumab

Children — 1st-line eculizumab

Normalization of Plt expected in < 7-10 d

Plt ≥150 G/L by day 7-10 → 3-6 m eculizumab treatment

Plt < 150 G/L by day 7-10 → Do not resume PE

Negative stool Stx PCR (not explained by antibiotic treatment or late stool collection) suggests aHUS

Differential diagnosis of aHUS

- ADAMTS13-deficiency TMA (TTP)
- STEC-HUS
- CbIC-defect TMA
- DGKe-HUS (< 2y age)
- Secondary HUS (malignancy, AID, drugs, infections) → Involvement of complement activation/dysregulation and impact of complement blockade poorly documented, requires further investigations

Check complement blockade (CH50<10%)
Check eculizumab concentration

If no trend towards increase in Plt :
Check for C5 polymorphism
Reconsider differential diagnosis

Anti-CFH antibodies-associated HUS

	Prognosis				
	Pre-complement inhibitors era			Complement inhibitors era[c]	
	PE	PE+IS	P value	Eculizumab	Eculizumab+IS
Risk of CKD stage 4-5 or death	36%[a,b]	14%[a]	<0.0001[a]	0/13	0/5
Risk of relapse	29-45%[a,b]	11%[a]	0.001[a]	0/13	0/5
Eculizumab withdrawal				3/13	4/5
Relapse after withdrawal				1/3	0/4

Outcome aHUS after ECU withdrawal

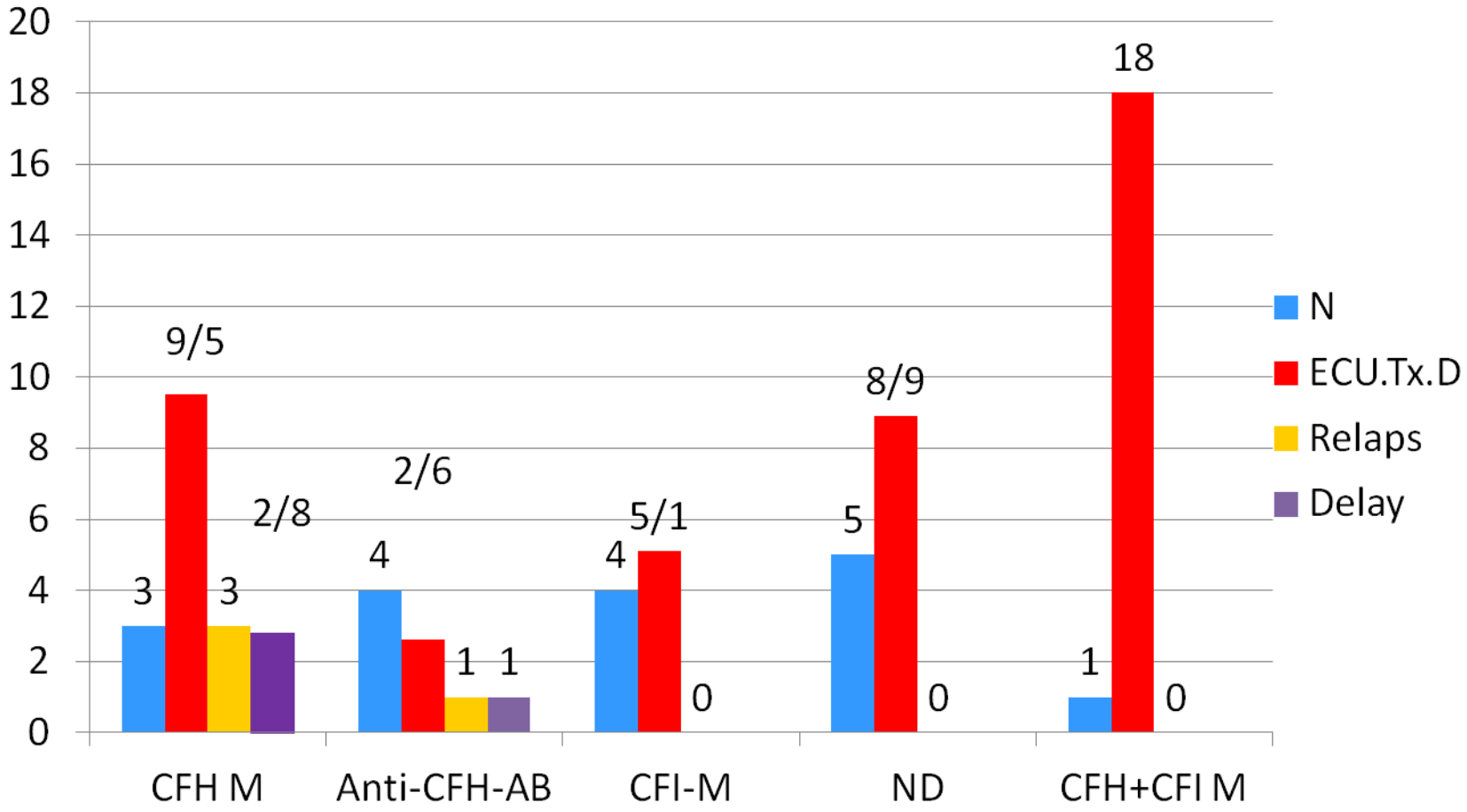
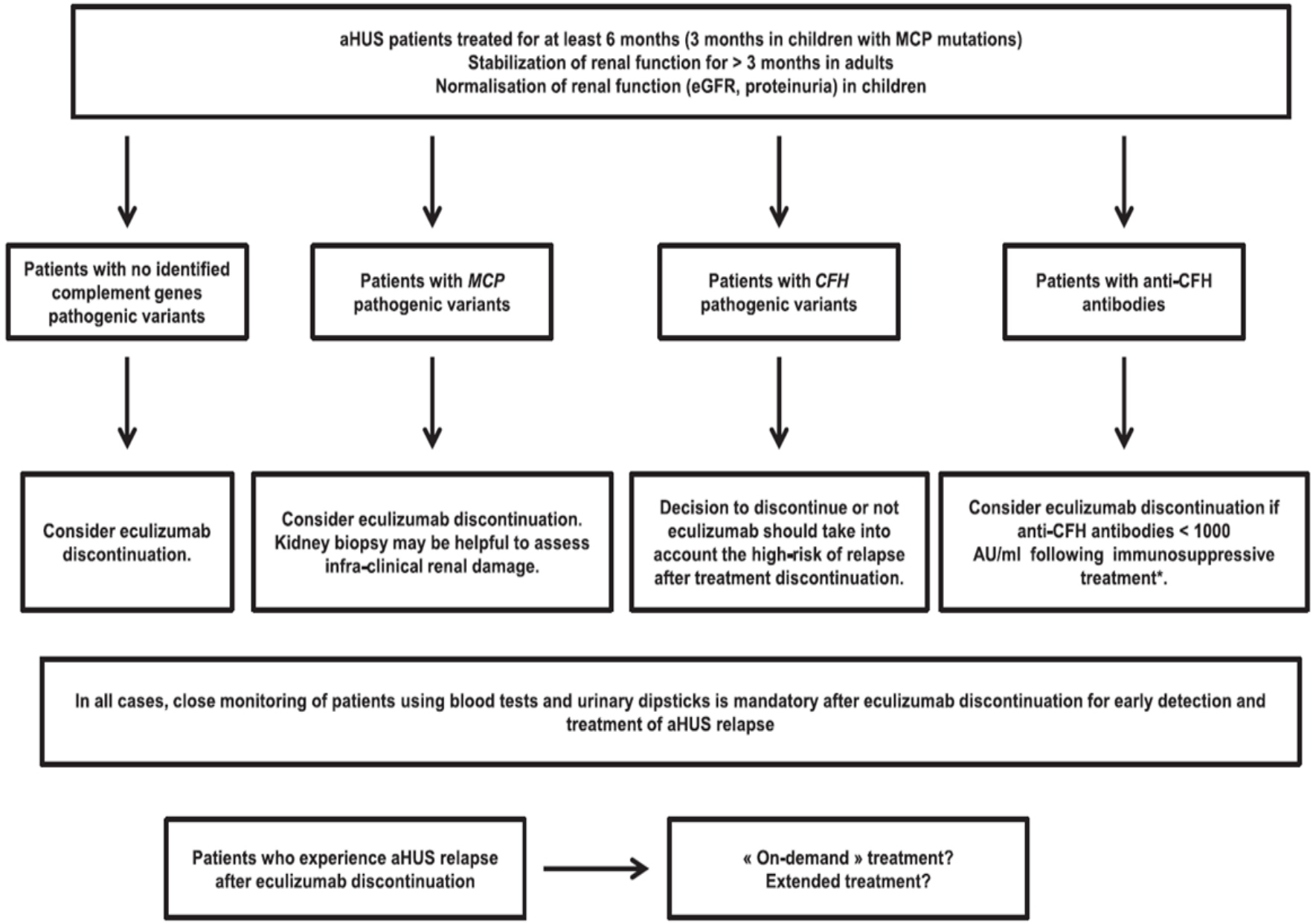


Table 3. Main characteristics of patients with atypical hemolytic uremic syndrome who relapsed or not after eculizumab discontinuation

Patient Characteristics	Relapsers, *n*=12	Nonrelapsers, *n*=26	*P* Value
Women	7 (58)	17 (65)	0.95
Age, yr			
Adults	25 (20–37)	36 (21–79)	0.02
Children	6 (2–9)	9 (5–17)	0.45
Patients with ≥1 aHUS episode before eculizumab use	6 of 12 (50)	3 of 26 (11)	0.03
HD at onset	6 of 12 (50)	12 of 26 (46)	0.89
Duration of eculizumab treatment, mo	14 (2–50)	14.5 (3–45)	0.95
SCr at eculizumab discontinuation, mg/dl			
Adults	1 (0.76–1.1)	1 (0.65–2.8)	0.55
Children	0.4 (0.25–0.45)	0.42 (0.4–0.44)	0.90
Variants			
CFH	8 (67)	3 (11)	0.002
MCP	4 (33)	4 (15)	0.20
No variant	0	16 (62)	<0.001
Follow-up after eculizumab discontinuation, mo	21.5 (15–38)	21.1 (5–43)	0.96

Values are shown as *n* (%) or as median (full range). aHUS, atypical hemolytic uremic syndrome; HD, hemodialysis; SCr, serum creatinine; *CFH, complement factor H; MCP, membrane cofactor protein.*

Proposed algorithm for eculizumab discontinuation in patients with atypical hemolytic uremic syndrome (aHUS).



Clin J Am Soc Nephrol 12: 50

Which Donor?

- Deceased or NRL Donor
  - Well informed R/D
  - ECU be available
- Related LD
  - Assess the risk of aHUS in donor
    - Mutation in R indisputable role / not found D
      - LOW risk for D-> **LRDTx**
    - D same mutation as R
      - High risk for D-> **LRDTx NOT DONE**
    - Role of variant in R uncertain
    - No mutation in R or D
      - Intermediate risk for D-> **LRDTX NOT DONE**

Prophylaxis ECU

- **High Risk** >> ECU
  - CFH,C3/CFB gain of function mutation
  - Prior graft lost due to recurrence whatever genetic mutation background
- **Intermediate risk** >> ECU or PE
  - CFI mutation
  - Combined MCP mutation
- **Low risk** >> No prophylaxis
  - DGKE mutation
  - Isolate MCP mutation
  - No mutation identified
  - Low anti-CFH antibody titer

Protection from endothelial damaging factors

- DGF/ IRI
  - Avoid
    - Prolonged cold ischemic time
    - Non-heart beating donor
    - Prefer young DD + preserved KF
    - Consider LD If possible
- Infection (CMV) >> CMV prophylaxis
- Immunosuppressive drugs
    - CNI not contraindication >> avoid over dose
    - CNI free mTOR based IS should be avoided
- HTN/ atherosclerosis
    - ACEI/ ARA/statins

When start ECU in high risk post-TX

- Prophylactic – non stop
- Withdrawal time?
- Further study in high risk mutation
- Adequate dosage – CH50: 0%

Any Question?

TABLE 25-2 **Recommendations for Treatment in Patients with Atypical or Recurrent HUS (Not Evidence Based)**

1.	Plasma exchange if infusion with fresh frozen plasma not sufficient or not tolerated.
2.	Pathogen-reduced FFP (Octaplas®) preferred, as mentioned in text.[167a]
3.0.	If complement is activated, intensive plasma exchange is warranted. In the first 2 weeks, 10-14 sessions with 40-60 ml/kg should be initiated. If not sufficient, increase to plasma volume of up to 420 ml/kg for 7 days.
3.1.	After the first 2 weeks (5-10 sessions), FFP volume 60-65 ml/kg per treatment.
4.	FFP volume during maintenance 20-25 ml/kg per week. This can be given as an infusion.
5.	Delay/avoid transplantation in patients with soluble complement disorders.
5.1.	Combined transplantations of liver and kidney may be an option in the future.
6.	Immunization program (including hepatitis A and B, varicella, influenza, and meningococci).