Risk factors of chronic renal failure after atypical Hemolytic Uremic Syndrome under plasmatherapy

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Urgences néphrologiques et Transplantation rénale

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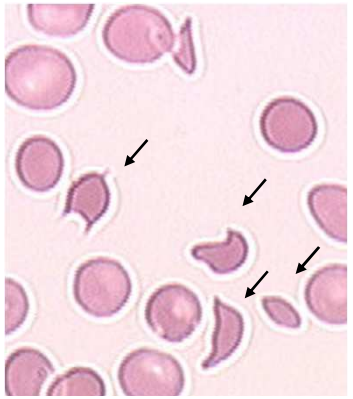
Thrombotic microangiopathies (TMAs)

TMA = a syndrome
There is not one TMA, but many forms of TMA

- **Microangiopathic hemolytic anemia (<12–13 g/dL)**
- **Peripheral thrombocytopenia (<150 x 10^9/L)**
- **Organ failure of variable severity**



TTP

- **Acquired**
- **Congenital**

4 cases/million/year

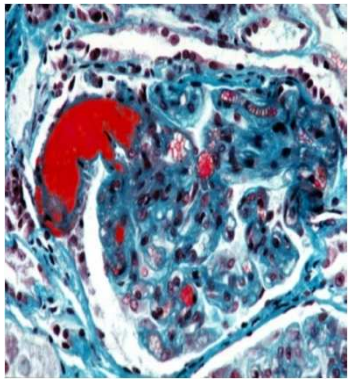
HUS

- **STEC**
- **Atypical**

2–4 cases/million/year

Other entities

- **HELLP syndrome**
- **CAPS**
- **Malignant HT**
- **Cancers**
- **Transplantation**



Mechanisms of the 9 TMA

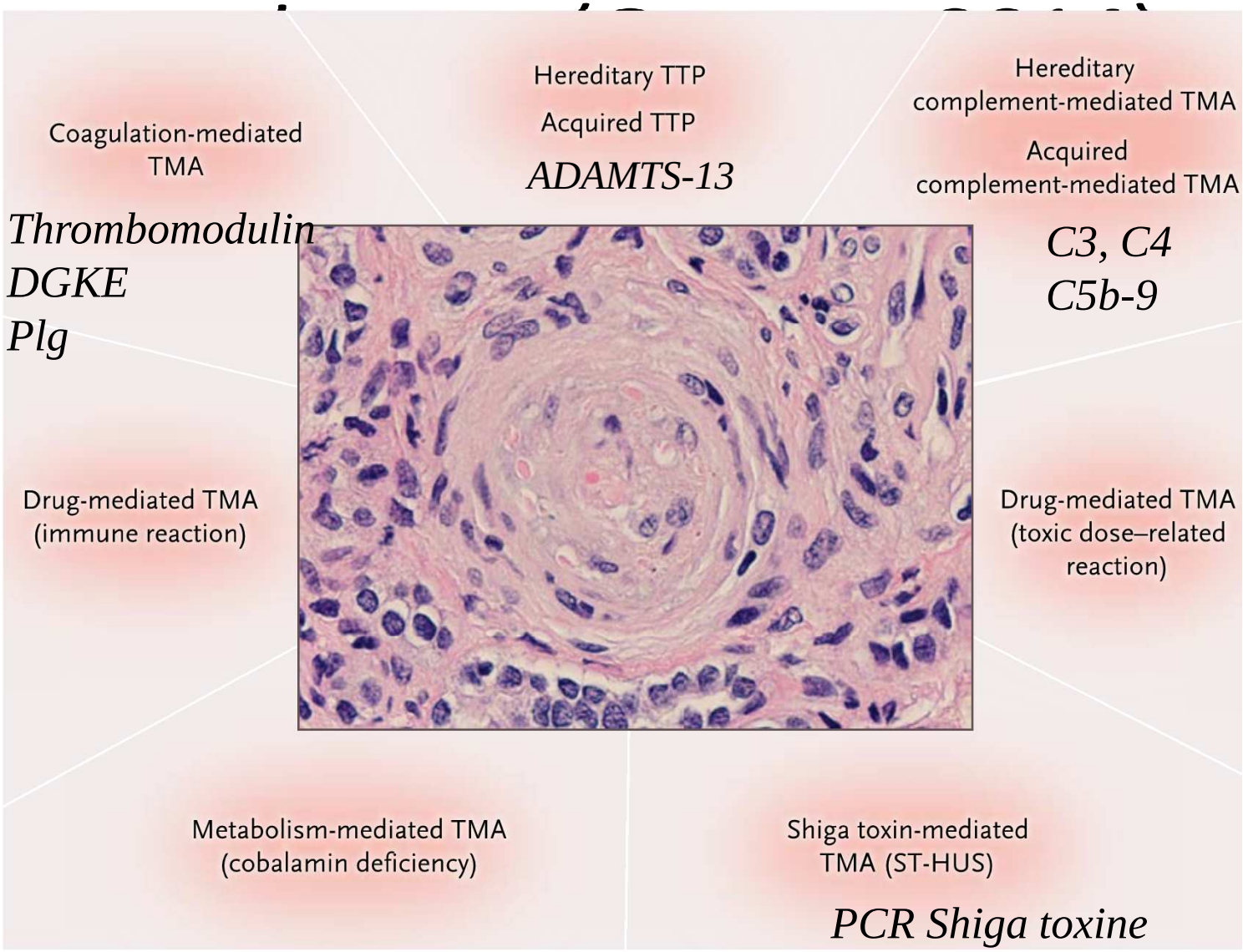
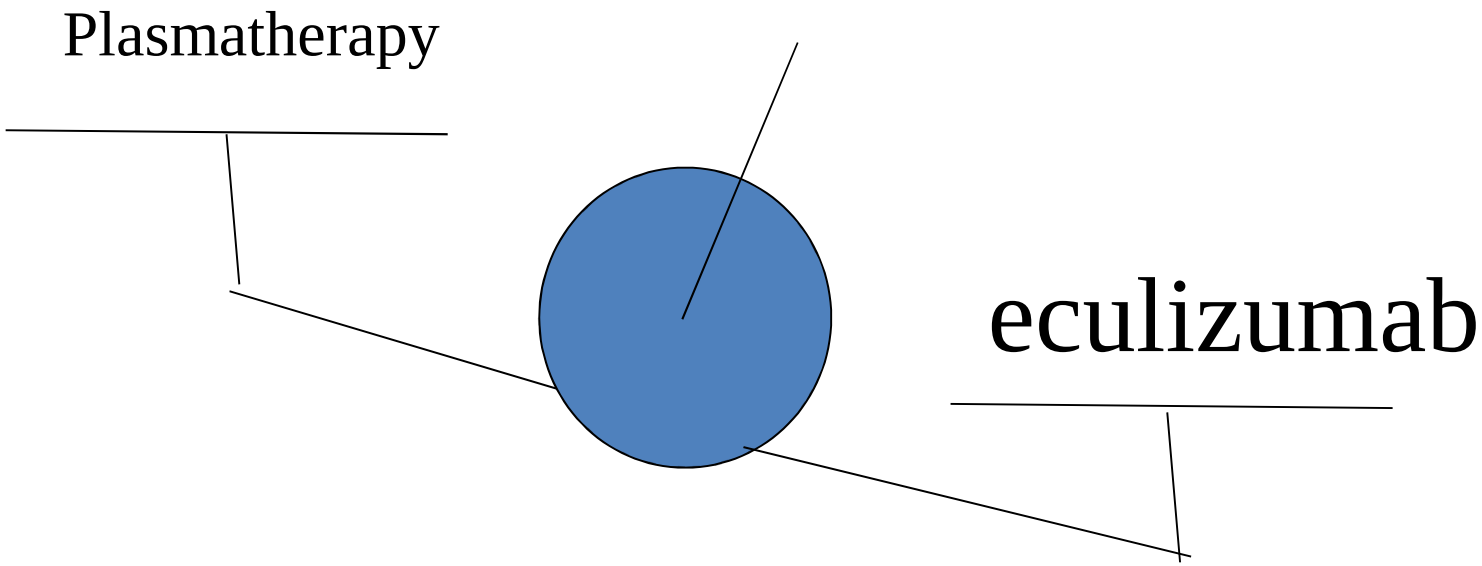


Table 2. Common Disorders Associated with Microangiopathic Hemolytic Anemia and Thrombocytopenia.*

Systemic infection
Systemic cancer
Severe preeclampsia, eclampsia, HELLP syndrome
Severe hypertension , with or without chronic nephritis
Autoimmune disorders (e.g., systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome)
Hematopoietic stem-cell or organ transplantation

George, NEJM, 2014

Which treatment for atypical HUS ? When and for which patients?



Prediction of the renal risk ?

Renal prognosis of aHUS

- Incidence of CKD and ESRD requiring dialysis after aHUS
- Risk factors for CKD after aHUS
- Prognostic score for CKD

Adult HUS: Patient characteristics:
55 patients (M/F) Mean age= 41 (19-88)

« Primary HUS »	15 (27%)
HIV-associated HUS	18 (33%)
Nephropathy-associated HUS	10 (18%)
Allotransplantation	7 (13%)
Cancer/leukemia	5 (9%)

(Tostivint, et al, NDT, 2002)

Treatments

- Anti hypertensive drugs
- Hemodialysis if needed
- Steroids: 0.5 to 1 mg/kg/day
- Plasma exchanges: 60 mL/Kg/day until platelet count > 150 000

Prognosis of HUS according to causes (1990 - 1998)

Causes	n	Death	survival	
			Normal RF	CRF ± HD
Primitive HUS	15	2 (12,5 %)	10(68,7%*	3 (18,7 %)
HUS and AIDS	18	8 (42,1 %)*	6 (36,8 %)	4 (21 %)
HUS on CKD	11	2 (18,2 %)	2 (18,2 %)	7 (63,6 %)
HUS after RT	7	0	2 (28,2 %)	5 (71,4 %)
Other HUS	4	1 (25 %)	1 (25 %)	2 (50 %)
Total =	55	13	21	21

* p< 0,02 compared to other groups

Adult HUS: In-hospital mortality (multivariate analysis)

Factors	$\chi 2$	P value	OR
HIV serology	7.8	0.0002	20.3
Hemodialysis	8.1	0.0004	35.7
Hemorragic complications	7.5	0.0062	200.3

(Tostivint, et al, NDT, 2002)

Adult HUS:
Renal prognosis at discharge

Factors	$\chi 2$	P value	OR
Nephropathies	5.37	0.02	99.6
LDH level	5.82	0.016	10.7
Fever	4.52	0.033	0.11
Haemodialysis	3.51	0.06	10.7

(Tostivint, et al, NDT, 2002)

Adult HUS: causes and prognosis in the last decade

Studies	1992a	1992b	1996a	1996b	1998	1999a	1999b	2002
No	43	53	52	28	45	126	22	55
Renal biopsy	0	0	0	28	30	0	0	49
Plasma therapy	67%	50%	Most !	?	65%	98%	72%	78%
CRF Mortality	14%	15%	8%	10%	7%	10%	45%	9% (23)

(Tostivint, et al, NDT, 2002)

Clinical presentation of aHUS in the french cohort

V. Frémeaux-Bacchi, CJASN, 2013

Table 1. Patients' characteristics at onset

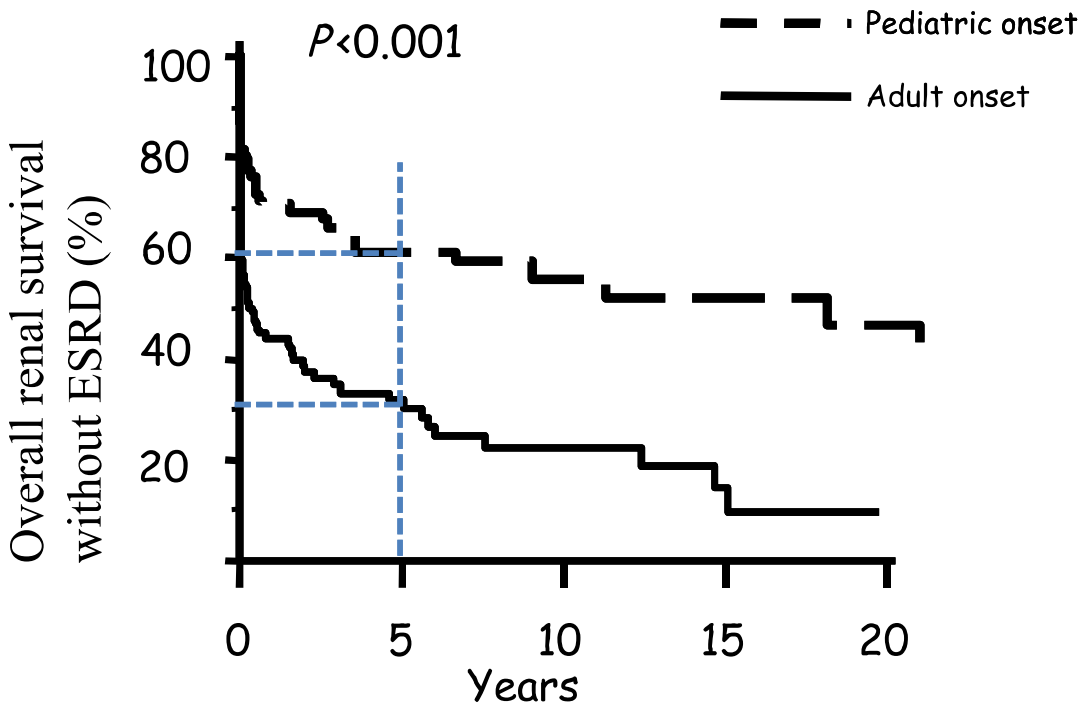
Characteristic	Children	Adults	*P* Value
Patients (*n*)	89	125	
Female/male (*n*/*n*)	42/47	93/32	<0.001
Mean age at onset (yr)	1.5 (0 to <15)	31 (15–85)	
Familial HUS history, *n* (%)	24 (26.9)	18 (14.4)	0.02
Triggering events, *n* (%)	42 (47)	41 (33)	0.03
Diarrhea	35 (39)	19 (15)	<0.001
Respiratory infections	7 (8)	1 (1)	0.03
Pregnancy		18/93 females (19.3)	
Neurologic involvement, *n* (%)	14 (16)[a]	10 (8)	0.08
Mean serum creatinine (μmol/L)	257 (28–990) (*n*=82)	640 (111–2408) (*n*=113)	<0.001
Dialysis required, *n* (%)	48/81 (59)	93/115 (81)	<0.001
Platelets count, *n* (%)			
$> 150 \times 10^9$/L	12/81 (15)	15/93 (16)	0.78
100–150 $\times 10^9$/L	9/81 (11)	22/93 (24)	0.02
50–99 $\times 10^9$/L	26/81 (32)	31/93 (33)	0.84
$< 50 \times 10^9$/L	34/81 (42)	25/93 (27)	0.05
Mean hemoglobin (g/dl)	6.8 (3–12) (*n*=84)	7.2 (5–11.8) (*n*=93)	0.004
Hemoglobin > 10 g/dl, *n* (%)	5/84 (6)	10/93 (11)	0.16
Complete triad, *n* (%)[b]	60/81 (74)	77/93 (83)	0.11

Values are given as means with ranges in parentheses or as percentages. HUS, hemolytic uremic syndrome.

[a]In children, extrarenal manifestations also included pancreatitis (increase of pancreatic enzymes with or without clinical/radiologic signs) in six cases (7%), hepatitis (increase in hepatic enzymes) in five cases (6%), multiorgan failure in three cases (3%), intra-alveolar hemorrhage in two cases (2%), and pericarditis in one case (1%). Extrarenal manifestations other than neurologic are not documented in adults.

[b]Complete triad: hemoglobin < 10 g/dl plus platelet count < 150 G/L plus serum creatinine above the upper limit of normal.

Cumulative Kaplan-Meier estimates of the rates of patients without ESRD or death according to the age at onset

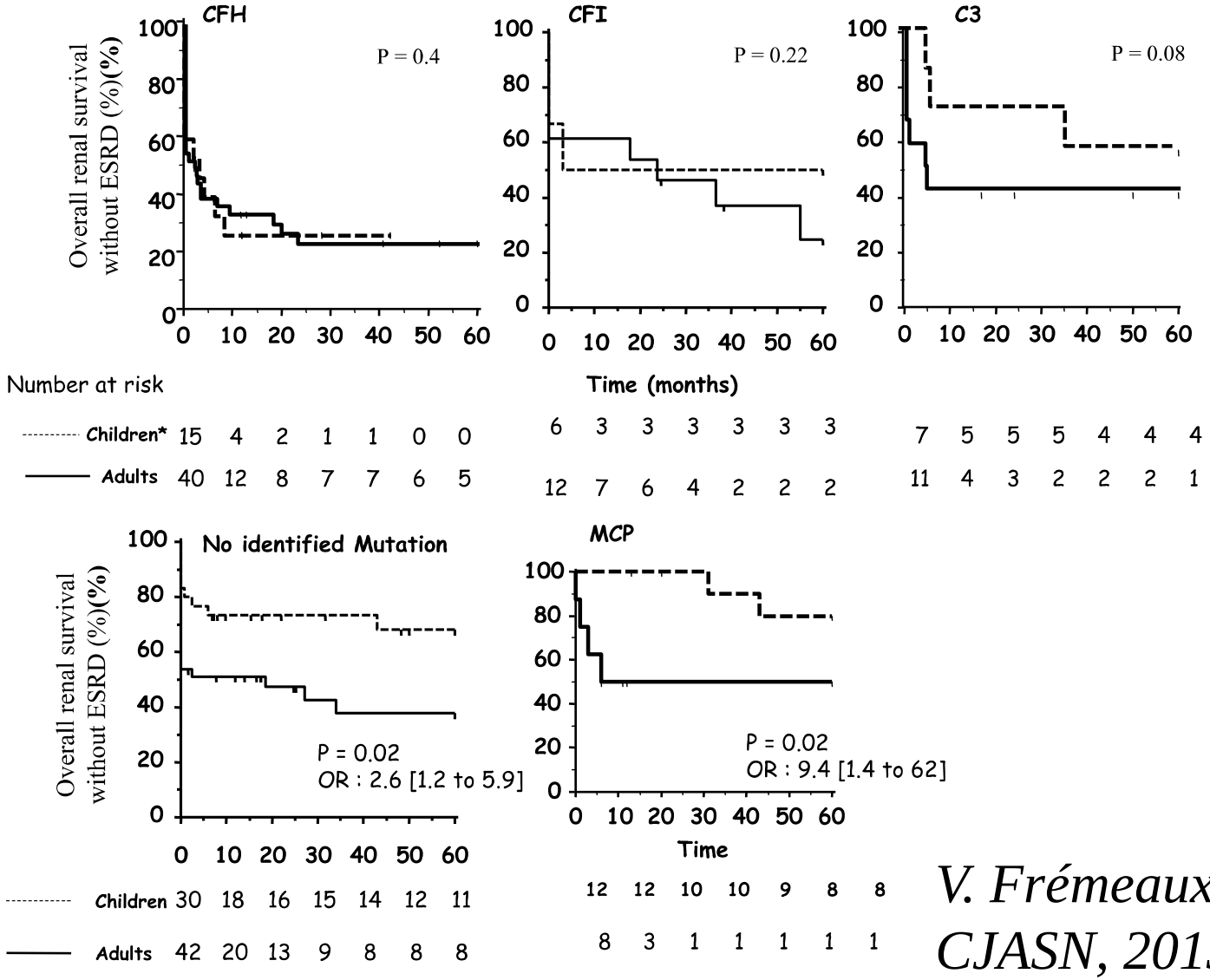


Number of aHUS patients at risk

Pediatric onset	89	34	17	13	6
Adult onset	125	18	7	2	0

V. Frémeaux-Bacchi, CJASN, 2013

Rates of patients without ESRD or death according to the genotype



V. Frémeaux-Bacchi, CJASN, 2013

Clinical and genetic aspects of aHUS (Italian cohort, Noris, 2010)

Screened Subjects

Sporadic patients	191	
Idiopathic	144	
Secondary:		
Malignancy and chemotherapy	1	
Malignant hypertension	14	
Post-transplant HUS[c] and calcineurin inhibitors	11	47
Pregnancy-related HUS	10	
Systemic disease	3	
Glomerulopathy	8	
Familial patients	82	
Overall patients	273	

Outcome after plasmatherapy according to genetic mutations (Italian cohort, Noris 2010)

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%)

Prognosis of aHUS
Italian cohort (Noris, 2010)

Alteration in	ESRF or Death (3 years)	Response to Plasma (outcome of episode = CR or PR/total of treated episodes)	Good Kidney Transplantation Outcome (at 1 year)
CFH	49 (77%)	57 (63%)	5 (29%)
CFI	6 (60%)	2 (25%)	2 (33%)
C3	8 (67%)	8 (57%)	4 (57%)
THBD	7 (54%)	7 (88%)	0
MCP	1 (6%)	28 (97%)	3 (100%)
CFH Ab	5 (63%)	9 (75%)	0
Non mut	60 (50%)	71 (69%)	12 (41%)
Sporadic	83 (49%)[a]	139 (69%)	19 (46%)
Familial	53 (74%)	43 (68%)	7 (30%)
Children	70 (48%)[b]	131 (78%)[c]	8 (33%)
Adults	63 (67%)	51 (53%)	18 (45%)

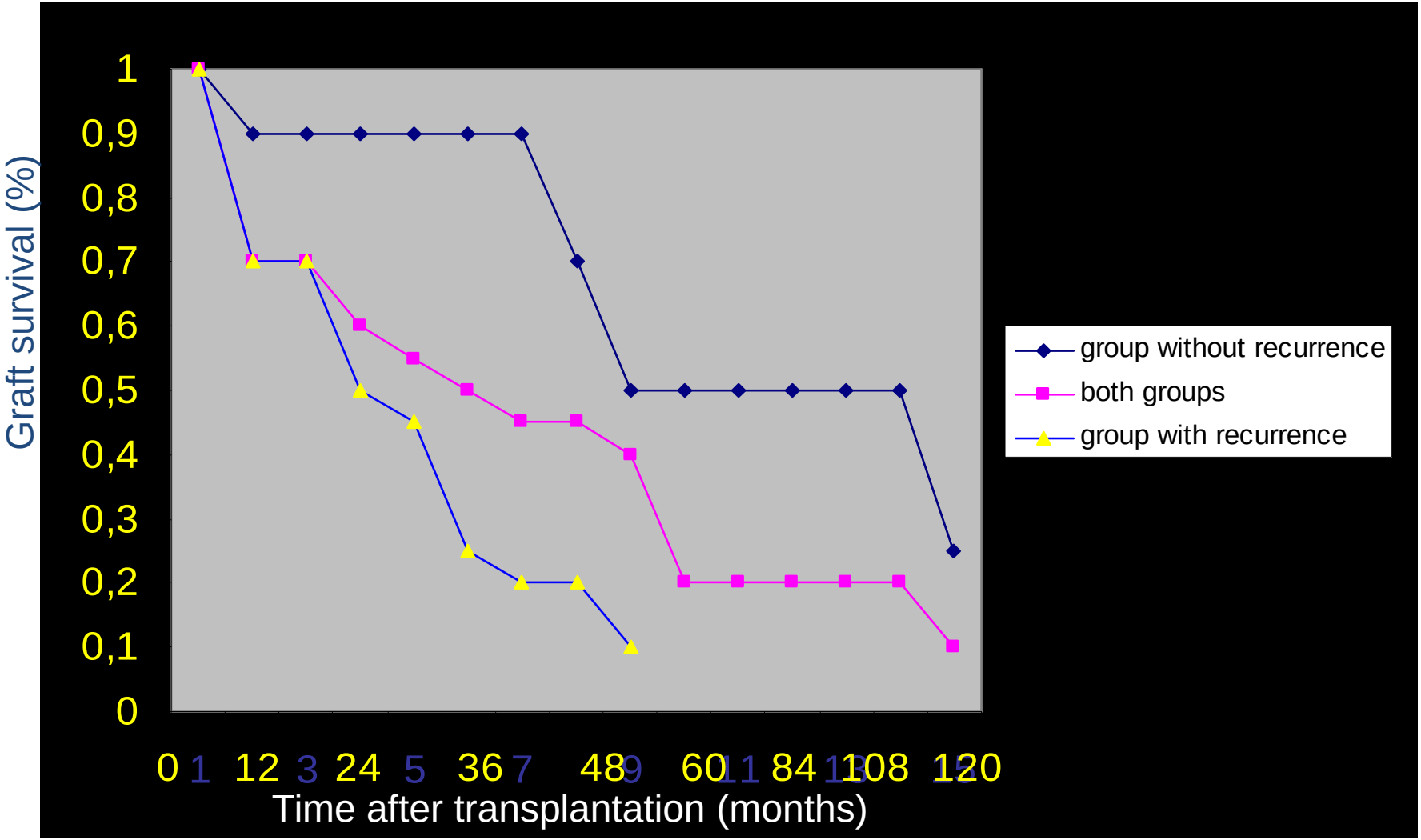
Frequency of the recurrence of HUS after transplantation

By patient :

- Definite recurrence : n = 9/16 (56 %)
- Possible recurrence : n = 4/16 (25 %)
    - *on 2 successive grafts (n = 3)
    - *at TR1, not at TR2 (n = 2)
    - *not at TR1 but at TR2 (n = 3)

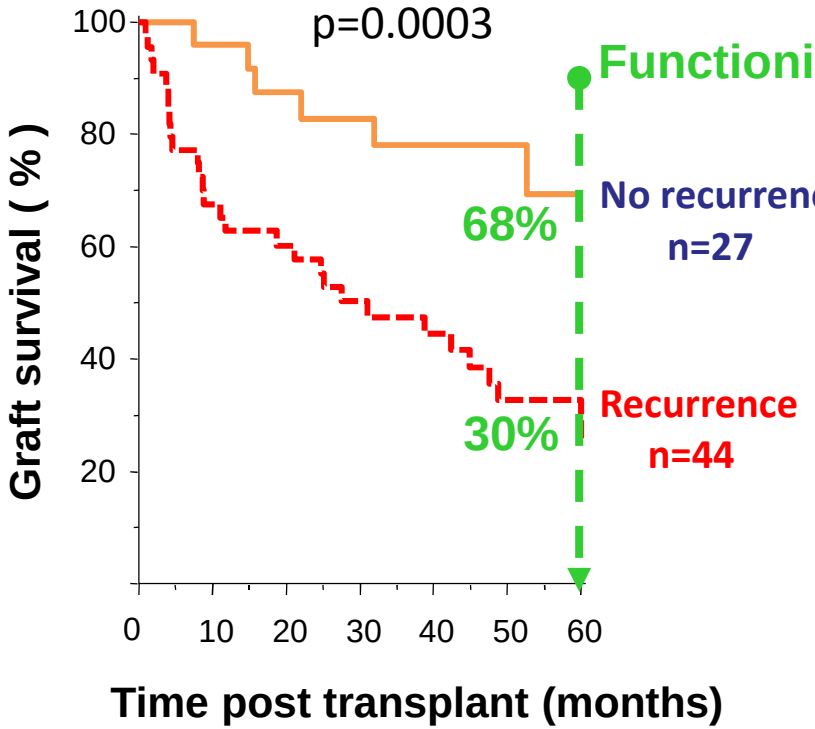
Lahlou, A , Medicine, 2000

Actuarial renal graft survival in 16 HUS patients who received 25 grafts



Lahlou et al, Medicine, 2000, 79 : 90-102

- **aHUS recurrence significantly impairs graft outcome**
- **Risk factors for recurrence are mostly, but not exclusively, genetic**



71 grafts in 57 patients

Risk factors for recurrence

- **Presence of a complement mutation (p=0.005)**
- **mTOR-inhibitor (p=0.03)**

} Multivariate analysis

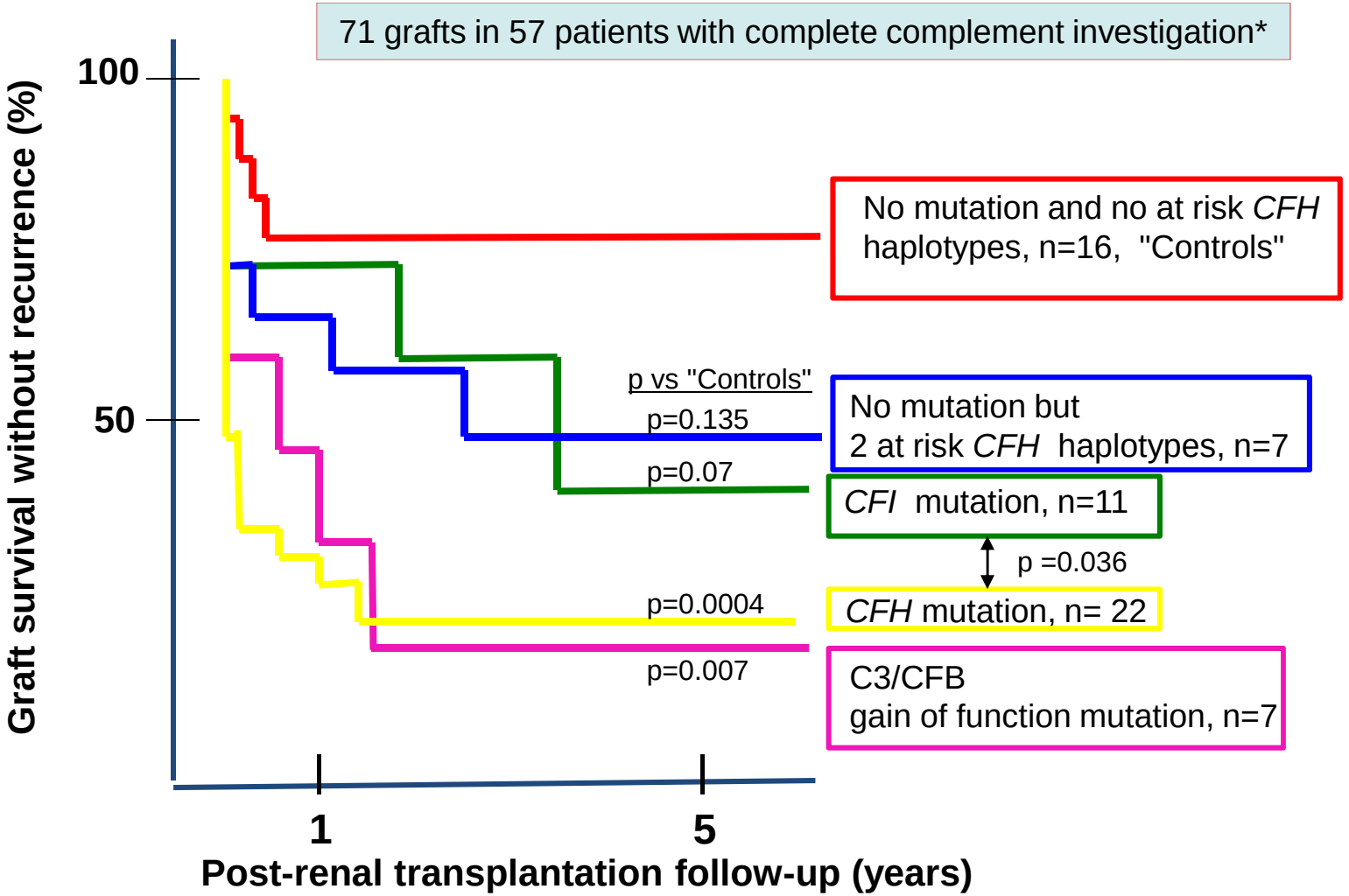
- Calcineurin inhibitor (p=0.27)
- Biopsy-proven acute rejection (p=0.66)

} Univariate analysis

At 5 years, graft survival was 30% in patients with recurrence versus 68% in patients without recurrence

Le Quintrec et al, AJT 2013

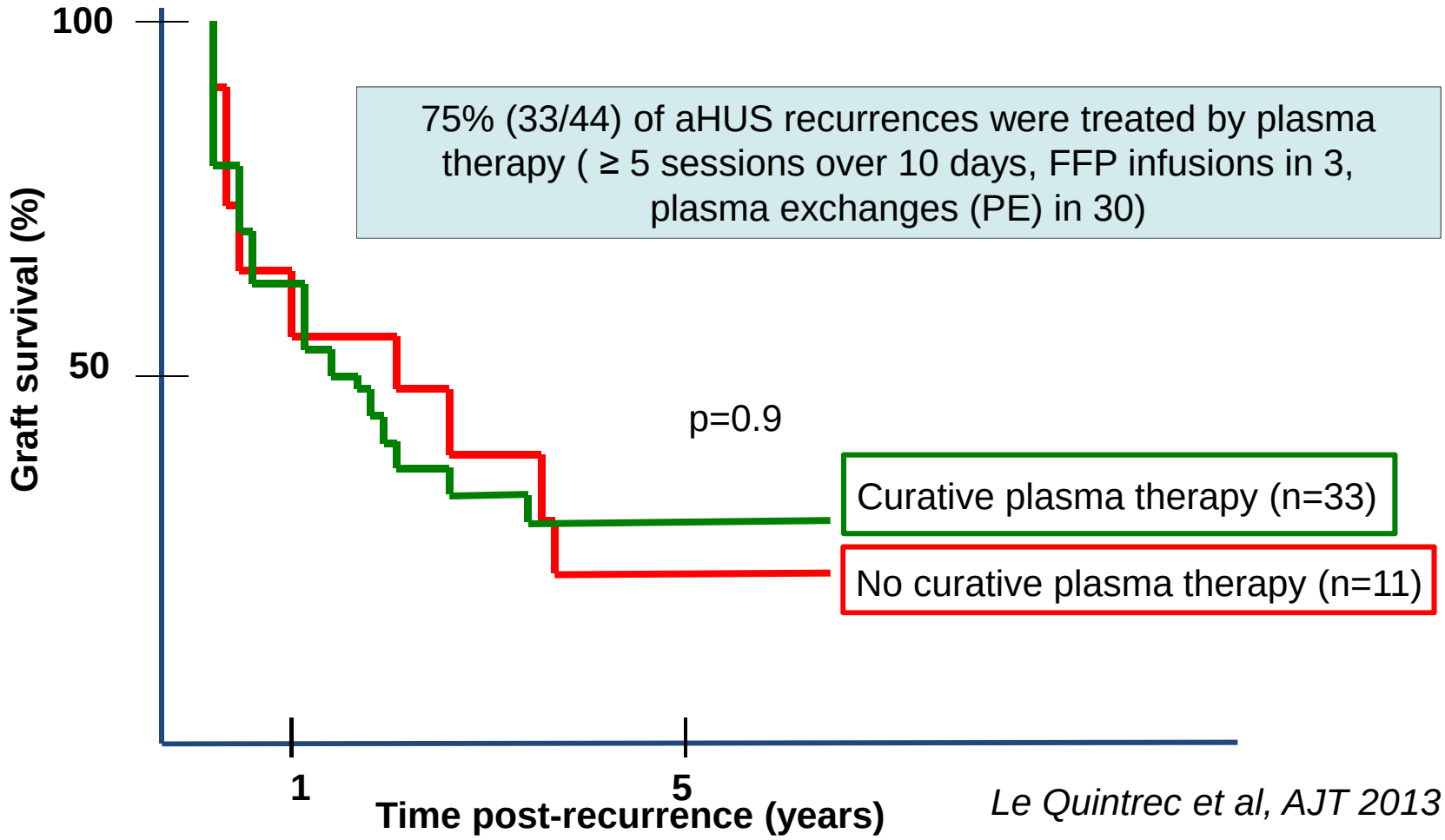
Pre-transplant assessment of post-transplant recurrence risk relies on genetics



**CFH* (sequencing and MLPA), *CFI*, *MCP*, *C3*, *CFB*, *THBD*, anti-CFH antibodies and at risk *CFH gtgt* haplotype

Le Quintrec et al, AJT 2013

aHUS and transplantation



Le Quintrec et al, AJT 2013

In most reports and series, curative plasma therapy failed to prevent graft loss

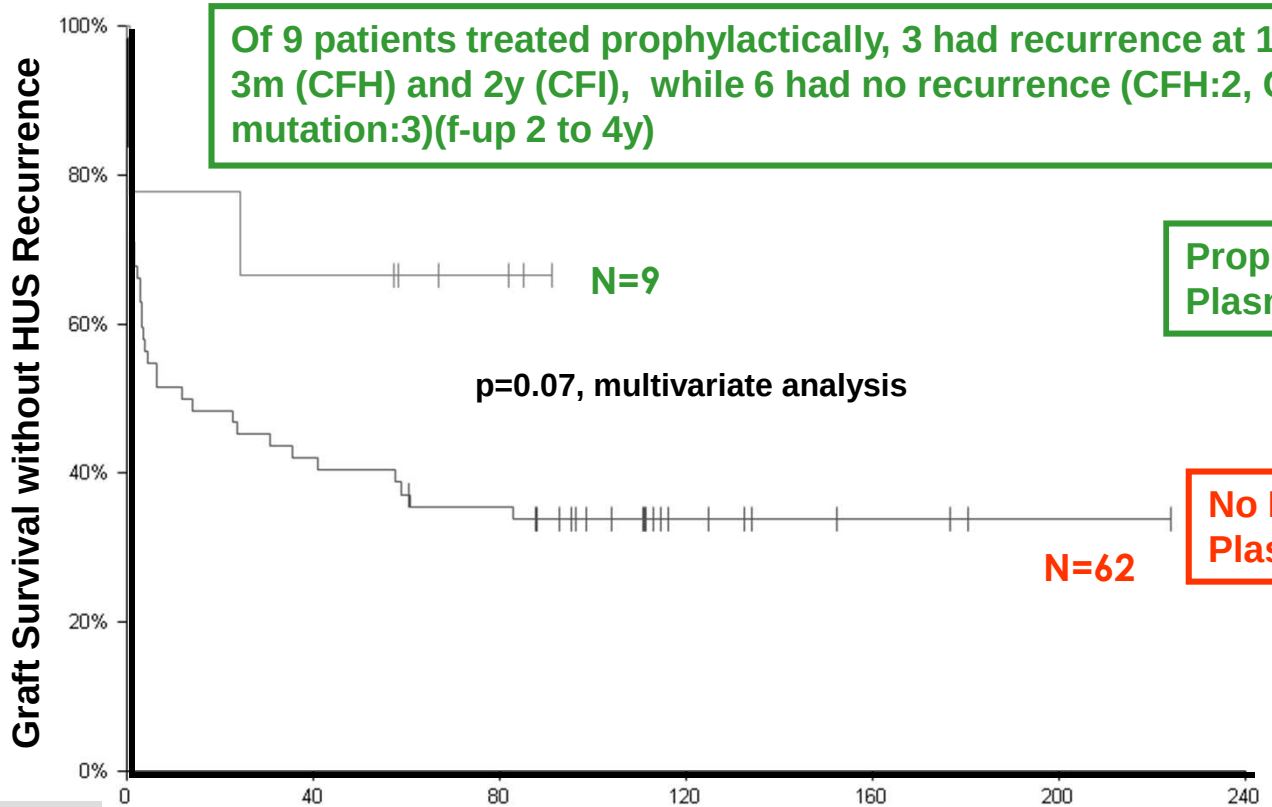
Noris, CJASN 2010; Loirat, Semin Thromb Hemost 2010,OJRD 2011; Zuber, Nat Rev Nephrol 2011

→ **Prophylactic plasma therapy (started before transplantation) recommended** (*Saland, JASN 2009*), **with scarcely documented efficacy**

Davin, AJKD 2009; Hirt-Minkowski, NDT 2009; Cruzado, AJT 2009; Albertazzi, Transplant Proc 2010; Zuber, Nat Rev Nephrol 2011

Potential benefit from prophylactic plasma therapy to prevent recurrence should not be discarded

Of 9 patients treated prophylactically, 3 had recurrence at 1m (CFH+CFB), 3m (CFH) and 2y (CFI), while 6 had no recurrence (CFH:2, CFI:1, no mutation:3)(f-up 2 to 4y)



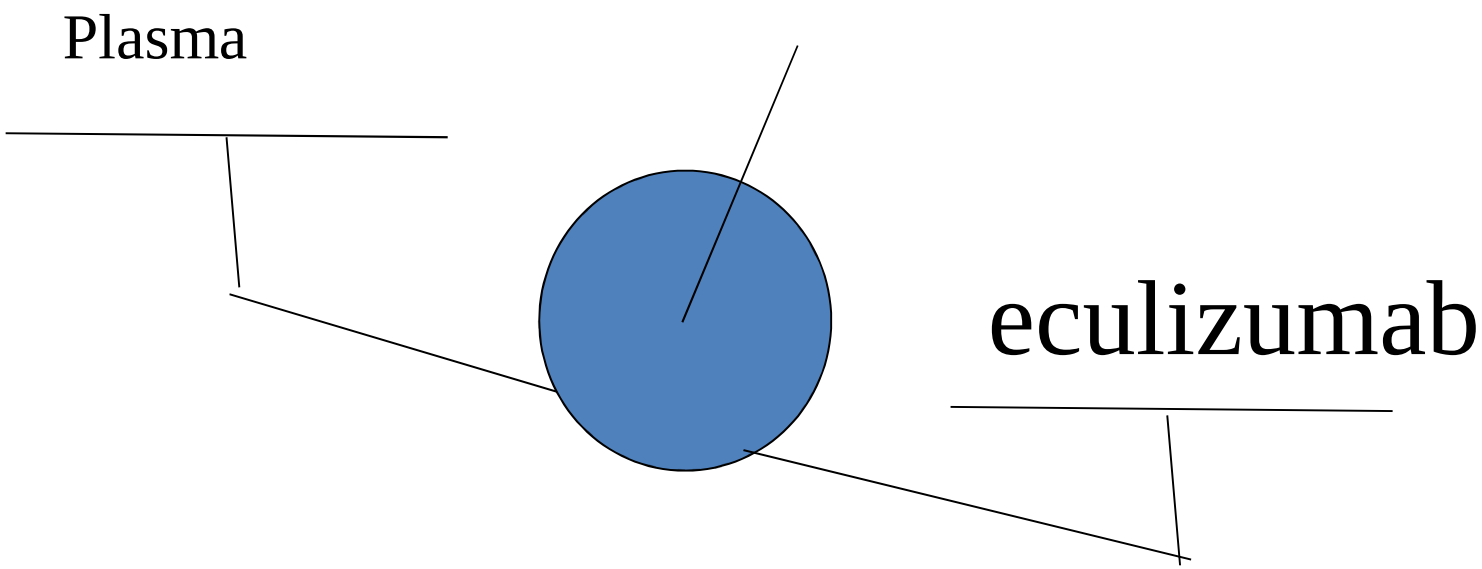
Number at risk

No Prophylactic Plasma therapy	62	31	27	24	22	15	8	5	4	2	2	1	1
Prophylactic Plasma therapy	9	8	7	5	4	0	0	0	0	0	0	0	0

PI in 5, PE in 4, started before surgery, daily x 5 to 10 days, then maintainance plasma therapy in 8 (PI in 6, PE in 2)

Le Quintrec et al, AJT 2013

Which treatment for atypical HUS ?
All aHUS ?
When to start?

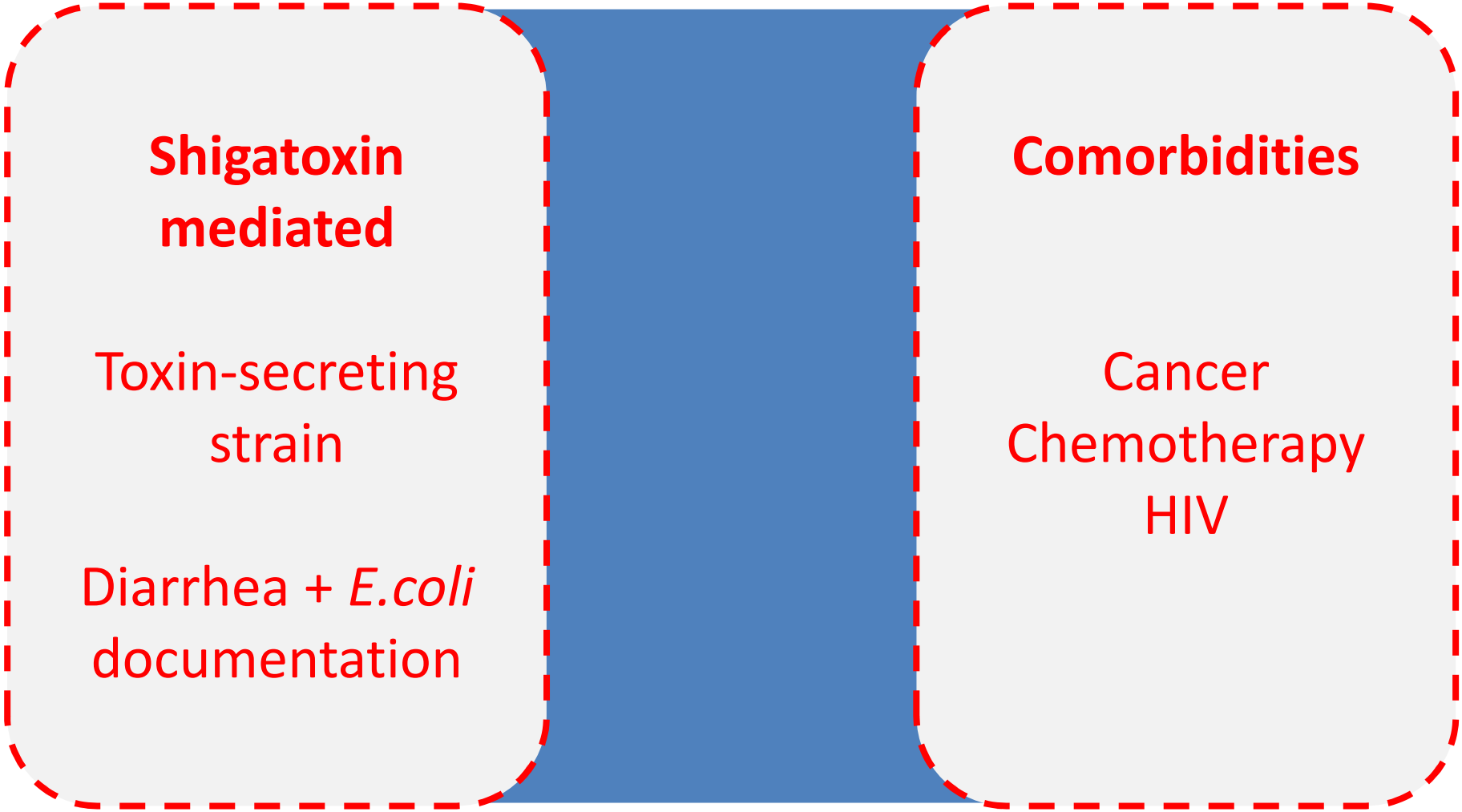


Prediction of the renal risk ?

Inclusion from the french registry of the national center for rare diseases

Age ≥ 18 years
TMA syndrome
AKI (SCr > 150µmol/L)
ADAMTS 13 > 20%

Exclusion


Shigatoxin mediated
Toxin-secreting strain
Diarrhea + *E.coli* documentation
Comorbidities
Cancer
Chemotherapy
HIV

Outcome

GFR (MDRD) < 45 mL/min/1.73m²

At M3, M6 and M12

		Cohort (N = 163)
Age (Median, quartiles range)		45.5 [31-65]
Sex (N,%)	Female	111 (68.1%)
Antecedents (N,%) :		
TMA syndrome (Pers. and/or Fam)		10 (6.2%)
Nephropathy		13 (8.1%)
Systemic disease	LED	2 (1.3%)
	Scleroderma	3 (1.9%)
	APS	1 (0.6%)
	Other	20 (12.2%)

Admission data

Arterial pressure (mm Hg)	**Systolic**	**150 [130-170]**
	Diastolic	**80.5 [72.25-95]**
	Mean	**106 [93-120]**
Abdominal	**Total**	**80 (50.6%)**
	Nausea and/or Vomiting	**44 (27%)**
	Diarrhea	**46 (29.3%)**
	Abdominal pain	**49 (31.2%)**
Neurological	**Total**	**78 (48.8%)**
	Headache	**28 (17.6%)**
	Convulsion	**35 (22%)**
	Confusion	**19 (11.9%)**
	Coma	**15 (9.4%)**
Renal	**Creatinine (µmol/L)**	**367.5 [204.5-622.25]**
	Hematuria (N,%)	**74 (81.3%)**
Hematology	**Hemoglobin (g/dL)**	**8.7 [7.05-10]**
	Platelets (G/L)	**58 [30.75-103.25]**
	LDH (N)	**4.5 [2.5-7.97]**
	Fibrinogen (g/L)	**3.9 [2.96-4.82]**

Outcomes

- **CKD: 46 %**
- **Death: 13 %**

Univariate

	CKD (54 patients)	No CKD (62 patients)	p
Nephropathy history	9 (16.7%)	2 (3.2%)	0.02
MAP (mmHg)	117 [105-131]	100 [90-113]	7 x 10-6
Initial RRT	47 (87%)	21 (33.8%)	6×10^{-9}
SCr (µmol/L)	613 [436-834]	297 [156-507]	2×10^{-7}
Hemoglobin (g/dL)	8.3 [6.9-9.5]	9.4 [7.4-10.5]	0.01
Platelets ($x10^9$/L)	91 [52-146]	49 [30-69]	5×10^{-5}
Proven infection	7 (12.9%)	22 (35.4%)	0.006
CH50 (%)	112 [81-120]	84 [57-100]	0.002
C4 (mg/L)	250 [199-317]	195 [98-299]	0.01

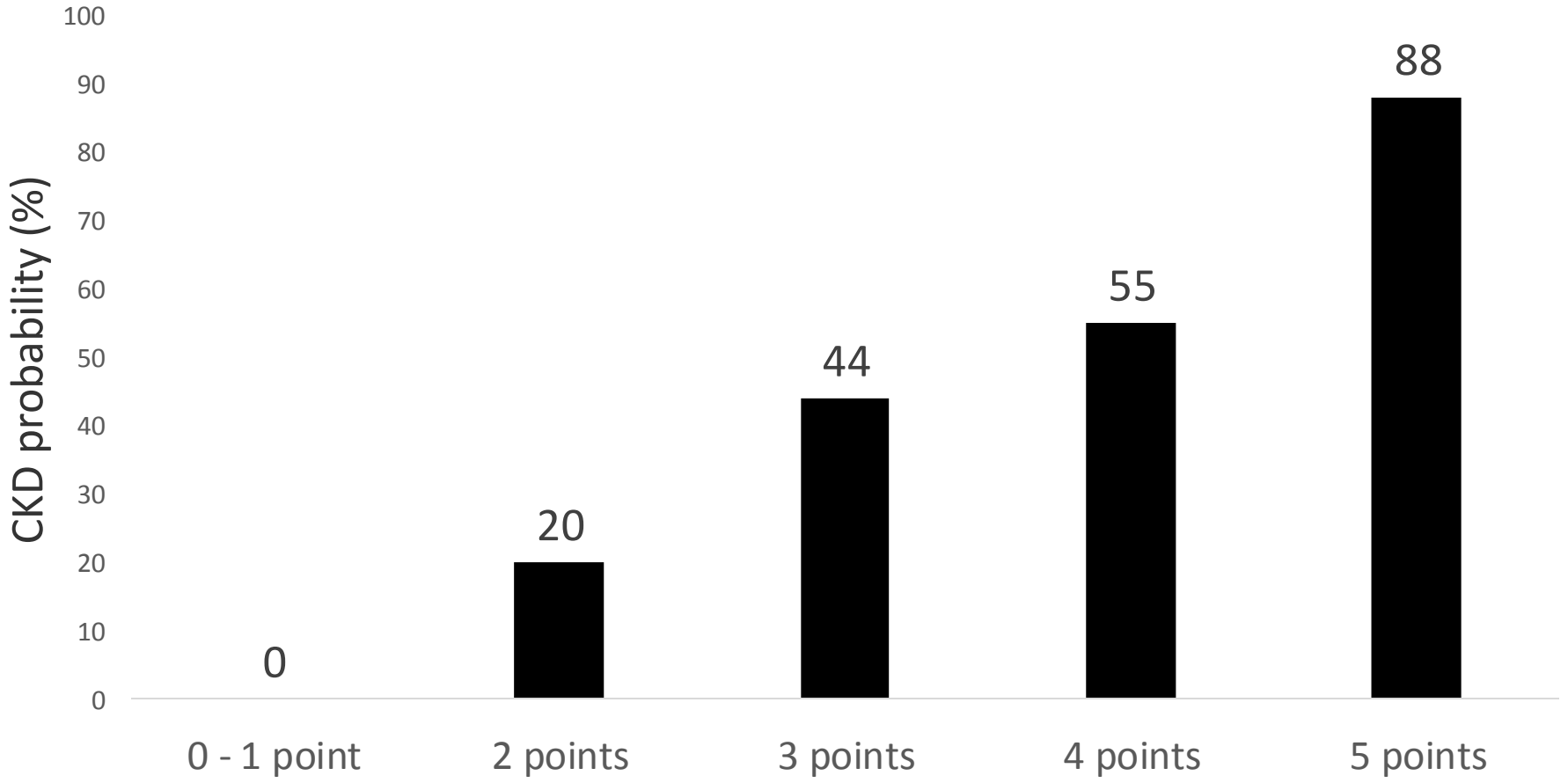
Multivariate analysis

	OR	IC	P
MAP (+10 mm Hg)	**1.74**	1.33-2.42	0.003
Platelets (+10 G/L)	**1.10**	1.03-1.19	0.002
SCr (+50 µmol/L)	**1.21**	1.10-1.35	0.009

Score

SCr (μmol/L)	
0-149	**0**
150-299	**1**
300-499	**2**
> 500	**3**
Platelets (G/L)	
0-59	**0**
> 60	**1**
MAP (mmHg)	
0-105	**0**
> 106	**1**

Score



Jamme, M, in preparation

Conclusions

- aHUS in adults has a poor prognosis with a 10% mortality rate and a 30 to 50% ESRD rate at 3 years
- Plasmatherapy may be effective on hematological parameters at the early phase but on the long run it cannot prevent CKD in about 70% of the cases
- High blood pressure at presentation, low platelet count, and severe renal failure are predictive of CKD
- The score may help to switch early from plasma exchanges to eculizumab