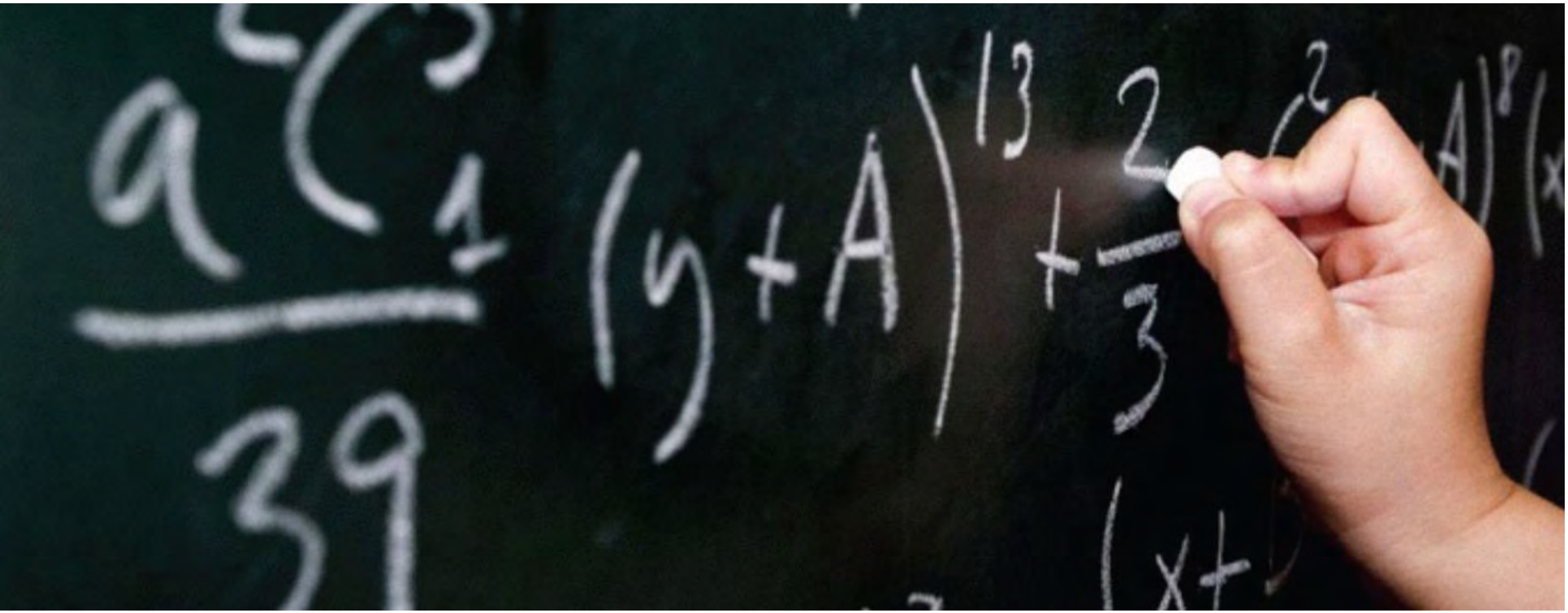
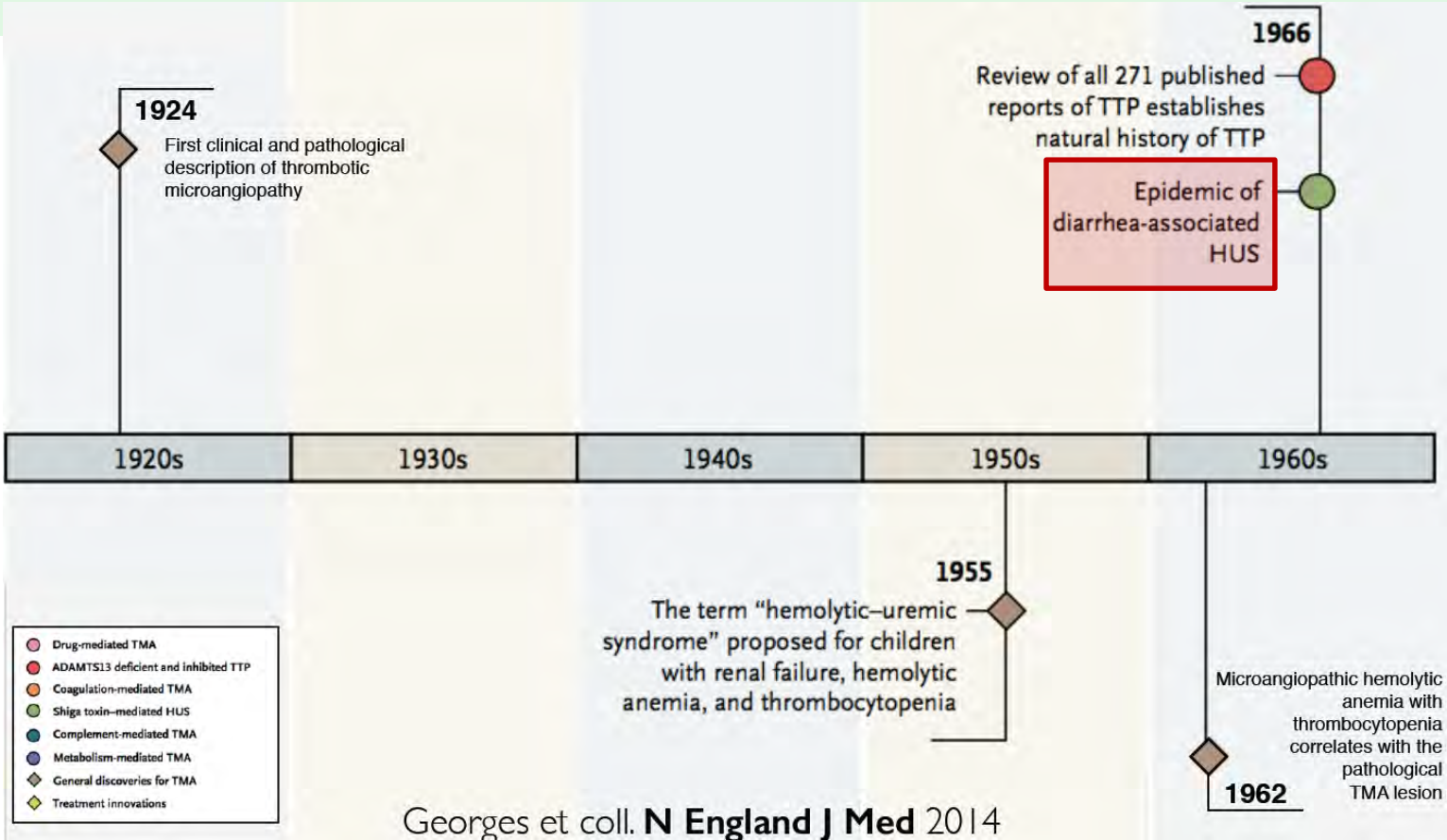


SHU, PTT: MATs and what else ?

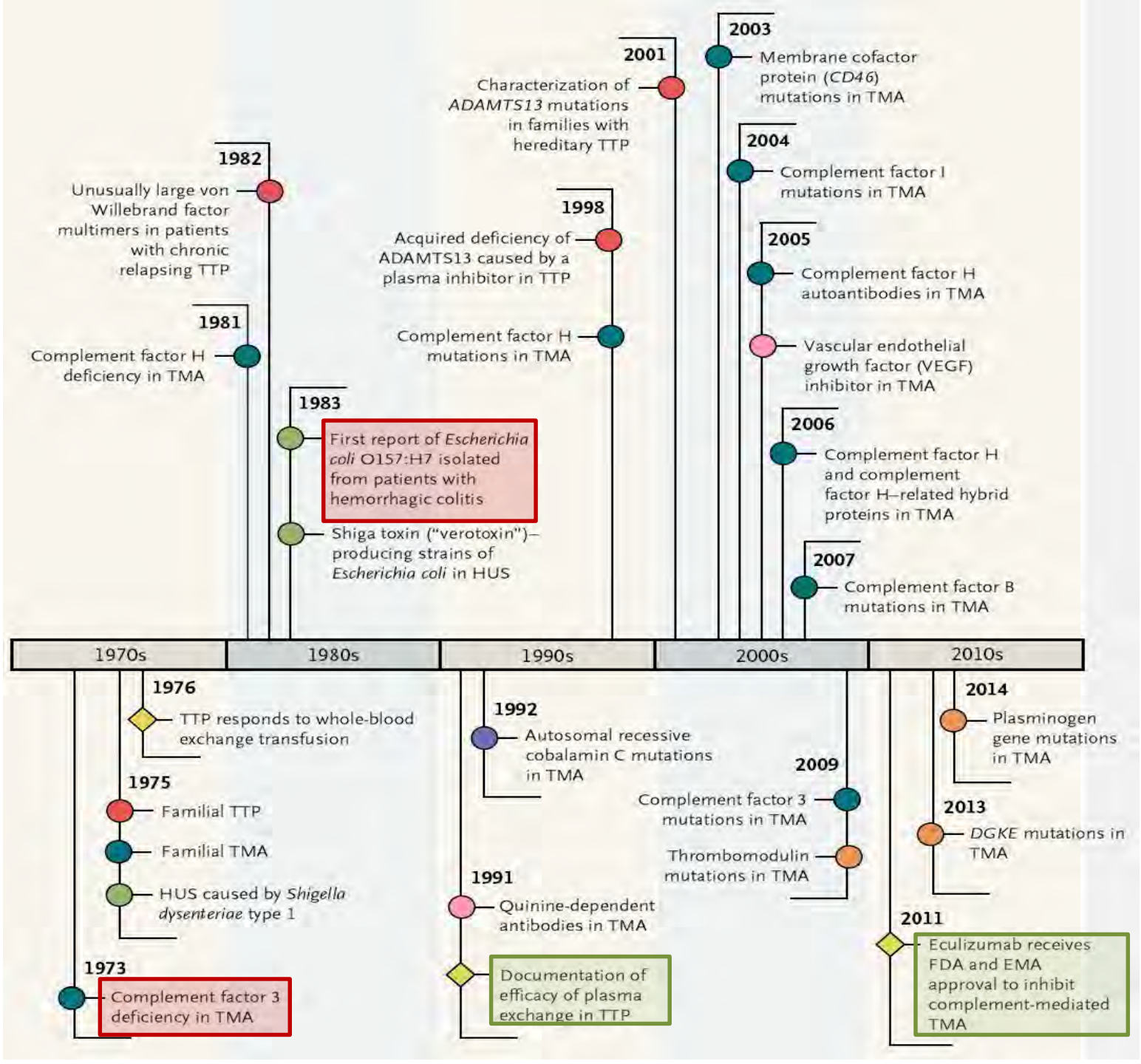
Dr Belén Ponte
Médecin adjointe agrégée
Service de néphrologie

Un peu d'histoire…

In 1924, **Moschcowitz** described a 16-year-old girl with weakness, pallor, purpura, and hemiparesis who died after 14 days with cardiac failure. Autopsy revealed hyaline thrombi in terminal arterioles and capillaries throughout most organs, includng the kidneys. This report was the first description of TMA, presumably TTP, also called ADAMTS13 deficiency–mediated TMA.



Georges et coll. **N England J Med** 2014


1970s
1980s
1990s
2000s
2010s
1973
Complement factor 3 deficiency in TMA
1975
Familial TTP
Familial TMA
HUS caused by Shigella dysenteriae type 1
1976
TTP responds to whole-blood exchange transfusion
1981
Complement factor H deficiency in TMA
1982
Unusually large von Willebrand factor multimers in patients with chronic relapsing TTP
1983
First report of Escherichia coli O157:H7 isolated from patients with hemorrhagic colitis
Shiga toxin ("verotoxin")–producing strains of Escherichia coli in HUS
1991
Quinine-dependent antibodies in TMA
Documentation of efficacy of plasma exchange in TTP
1992
Autosomal recessive cobalamin C mutations in TMA
1998
Acquired deficiency of ADAMTS13 caused by a plasma inhibitor in TTP
Complement factor H mutations in TMA
2001
Characterization of ADAMTS13 mutations in families with hereditary TTP
2003
Membrane cofactor protein (CD46) mutations in TMA
2004
Complement factor I mutations in TMA
2005
Complement factor H autoantibodies in TMA
Vascular endothelial growth factor (VEGF) inhibitor in TMA
2006
Complement factor H and complement factor H–related hybrid proteins in TMA
2007
Complement factor B mutations in TMA
2009
Complement factor 3 mutations in TMA
Thrombomodulin mutations in TMA
2011
Eculizumab receives FDA and EMA approval to inhibit complement-mediated TMA
2013
DGKE mutations in TMA
2014
Plasminogen gene mutations in TMA

Pour faire simple…

MAT

Micro**A**ngiopathies**T**hrombotiques

PTT

Purpura **T**hrombotique **T**hrombocytopénique

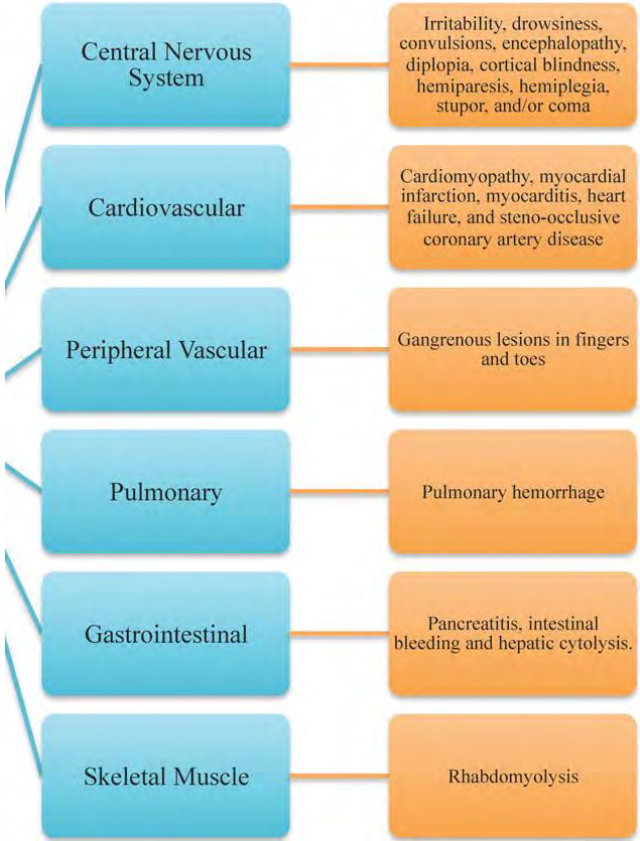
SHU

Syndrome **H**émolytique et **U**rémique

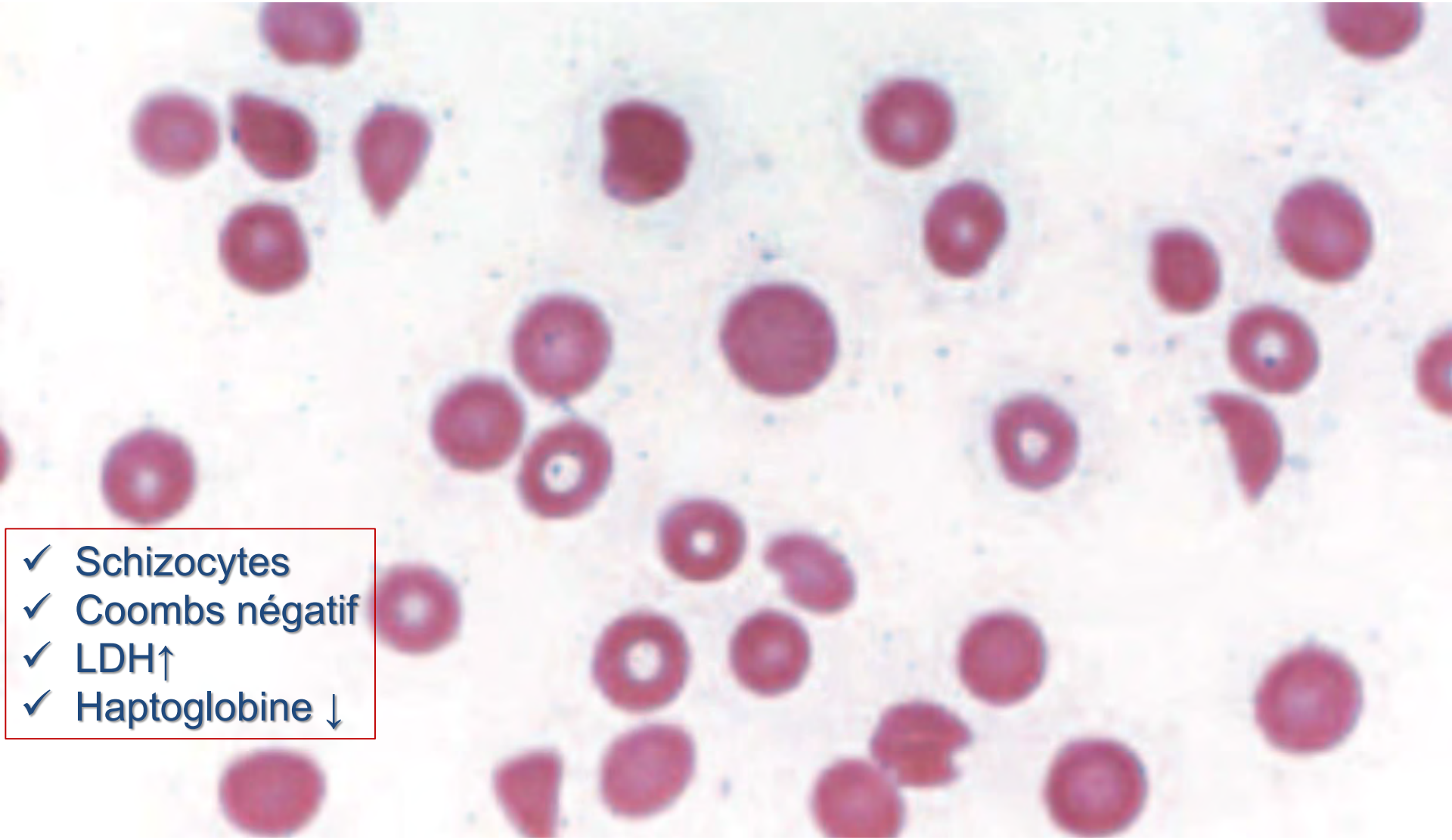
… mais nous allons voir que c'est un peu plus compliqué !

Clinique MATs…

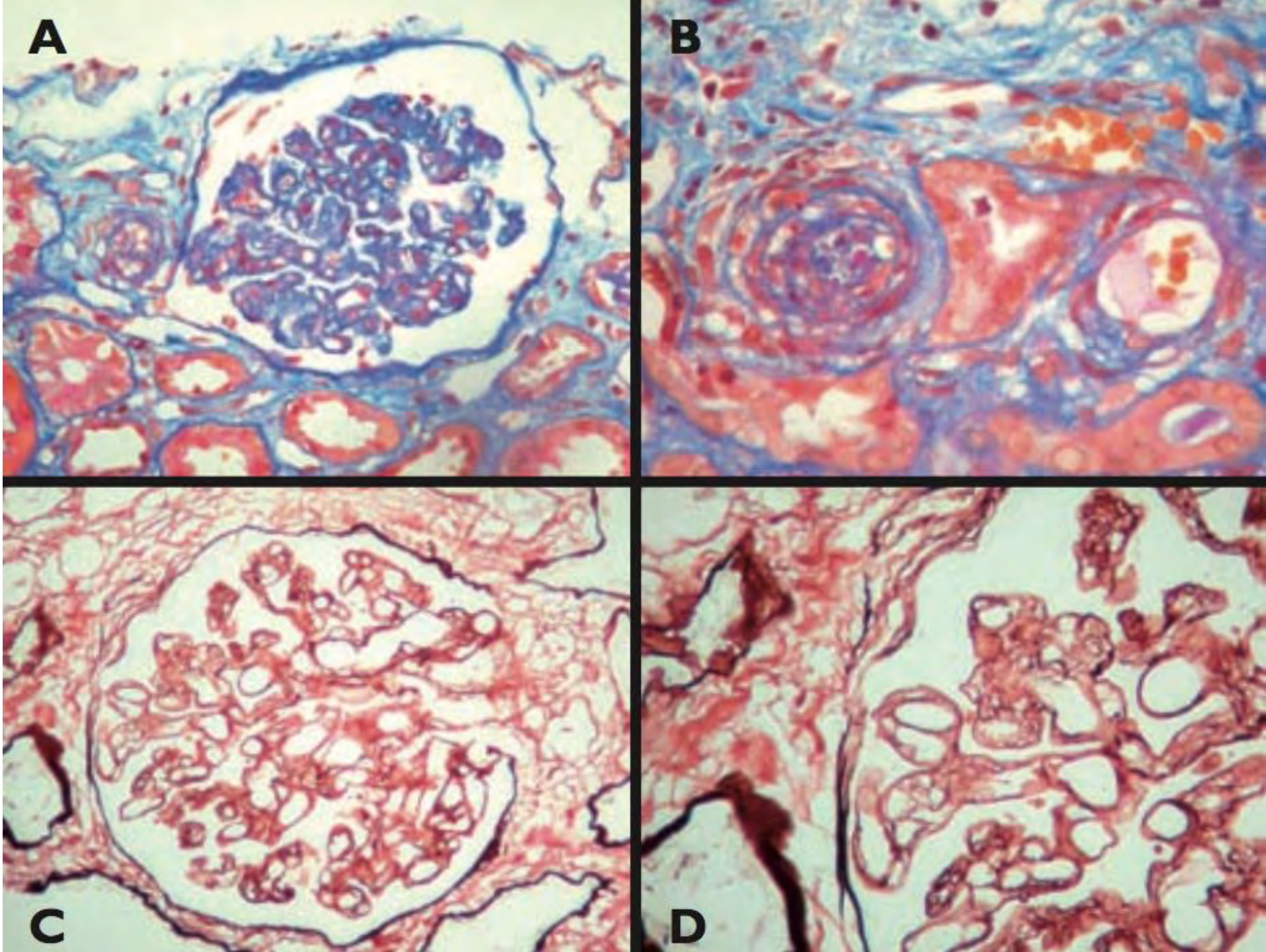
- ✓ Anémie hémolytique micro-angiopathique
- ✓ Thrombocytopénie
- ✓ Atteinte d'organe sur ischémie:
  - Rein (IRA, protéinurie)
  - Cerveau
  - Cœur
  - Foie, pancréas
  - Poumons
  - Yeux, peau



Anémie hémolytique…



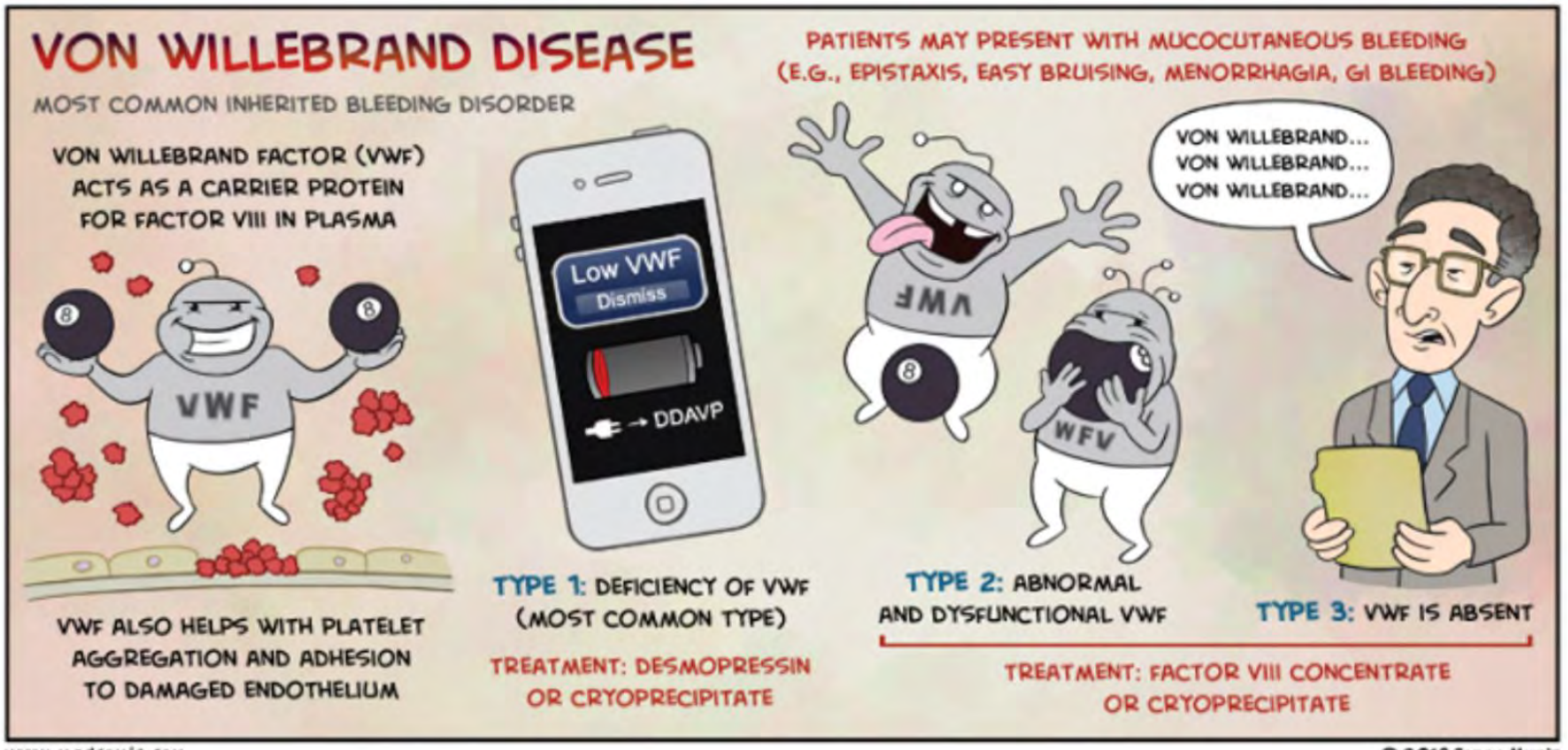
- ✓ Schizocytes
- ✓ Coombs négatif
- ✓ LDH↑
- ✓ Haptoglobine ↓


A
B
C
D

PurpuraThrombotiqueThrombocytopénique

FvW nécessaire à l'agrégation plaquettaire.
Protéine ADAMTS13 clive multimères FvV.

Sans ADAMTS13: multimères → micro-thrombi capillaires + artérioles



PurpuraThrombotiqueThrombocytopénique

Forme typique:

EF, atteinte cérébrale, anémie hémolytique, thrombocytopénie, IRA (rare)

✓Acquis (ac inhibant activité ADAMTS13)

2.9 cas/1mio/an chez adulte

0.1 cas/1mio/an enfant

F+: âge (18-50ans), ethnie africaine, genre féminin

Activité ADAMTS 13 <10% = suggestif!

✓Héréditaire (mutations)

PTT: traitement

- ✓ Echanges plasmatiques avec PFC (PEx)

  1-1.5 volume plasma échangé

  5-7 jours de suite afin de voir évolution

  selon sévérité 2x/j !

  Si pas de disponibilité PEx→ infusion PFC

- ✓ Hautes doses stéroides

- ✓ Traitement adjuvant:

  Rituximab: + ↓ nb de PE, - réponse médiane après 10j

  ? Dose 375mg/m2 1x/sem , 1g 1x/2sem?

Scully M. BJ hematology 2012
Scully M. BJ hematology 2007
Scully M. Blood 2011

Syndrome Hémolytique Urémique

Classiquement distingue Typique vs Atypique

Typique: dans contexte diarrhée, épidémie

- ✓ Associé principalement à E Coli 0157:H7
- ✓ Autres bactéries entéro-toxiques (S dysenteriae)

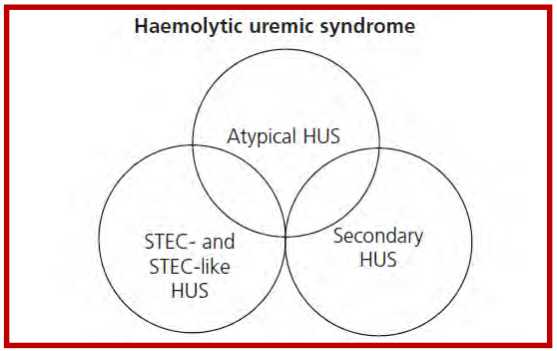
→ libération shigatoxines ou shiga-like toxines

→ transportées par PMN jusqu'à cellules endothéliales micro-circulation rénale (tropisme)

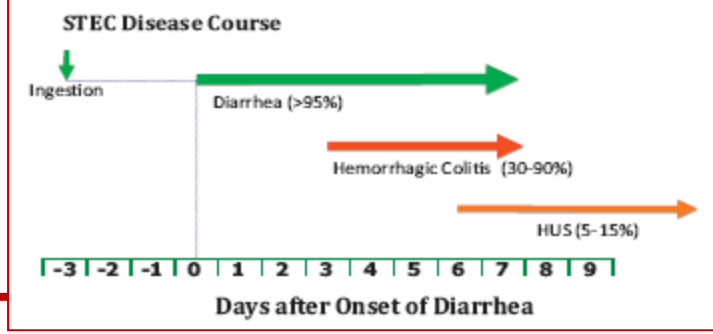
→ Activation / mort c. endothéliales → micro-thrombi

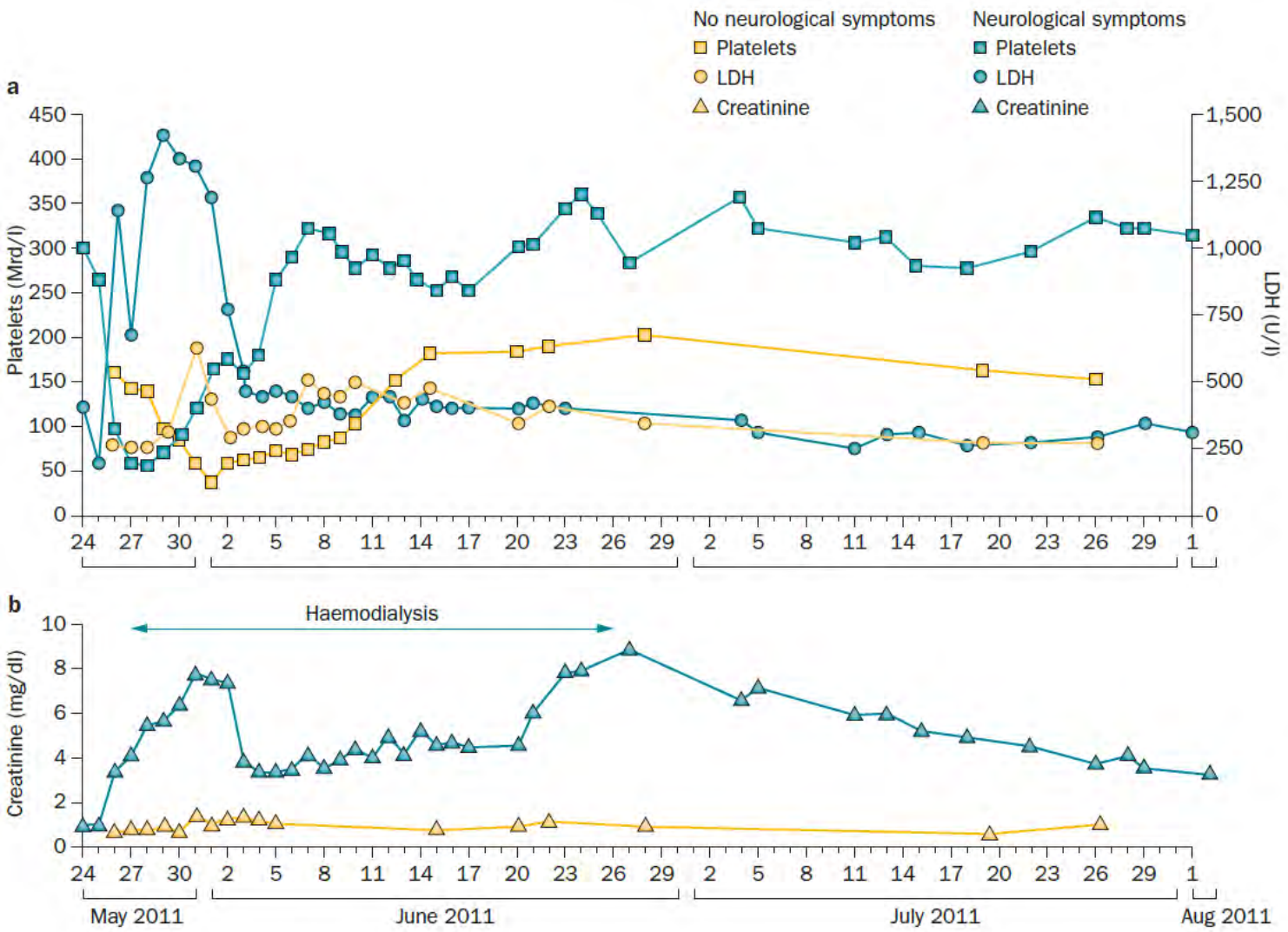
Atypique: en dehors de diarrhée

- ✓ Peut être idiopathique ou secondaire



SHU « typique »

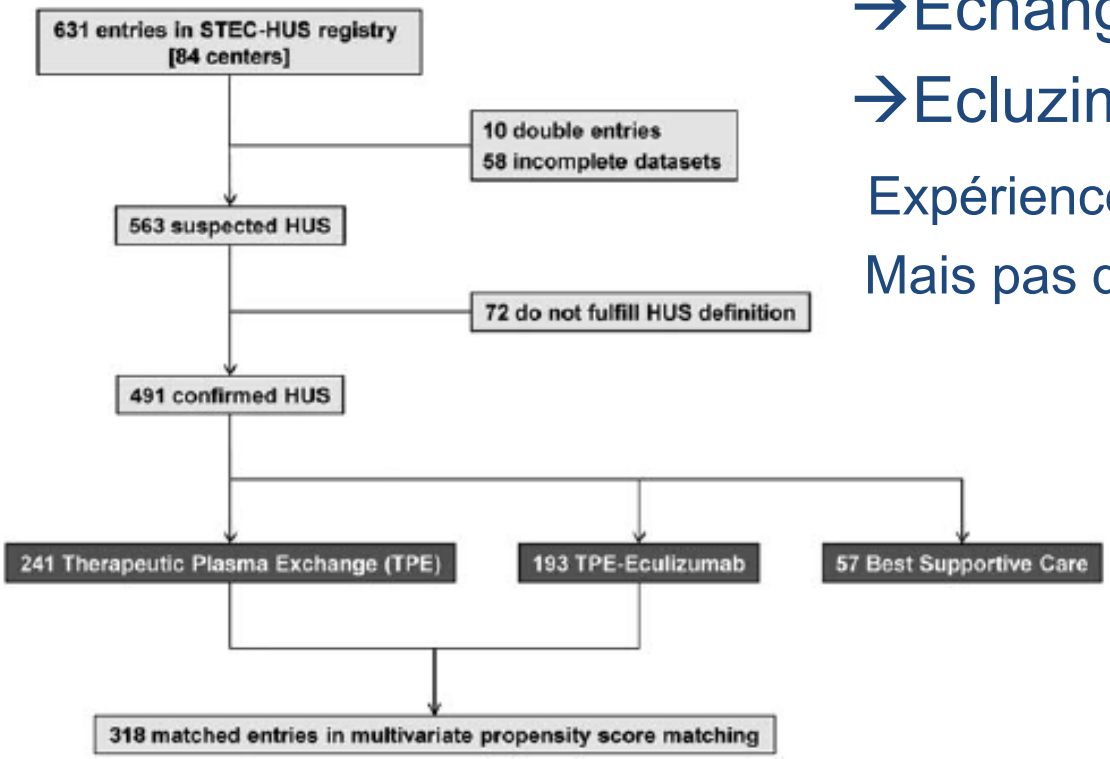

STEC Disease Course
Ingestion
Diarrhea (>95%)
Hemorrhagic Colitis (30-90%)
HUS (5-15%)
-3 -2 -1 0 1 2 3 4 5 6 7 8 9
Days after Onset of Diarrhea


a
No neurological symptoms
Platelets
LDH
Creatinine
Neurological symptoms
Platelets
LDH
Creatinine
Platelets (Mrd/l)
LDH (U/l)
b
Haemodialysis
Creatinine (mg/dl)
May 2011
June 2011
July 2011
Aug 2011

SHU « typique »: Traitement

✓ Traitement de soutient!

Dans cas sévères, à discuter mais pas « evidence-based » et controverses



→Echanges plasmatiques

→Ecluzimab (inhibiteur C5)

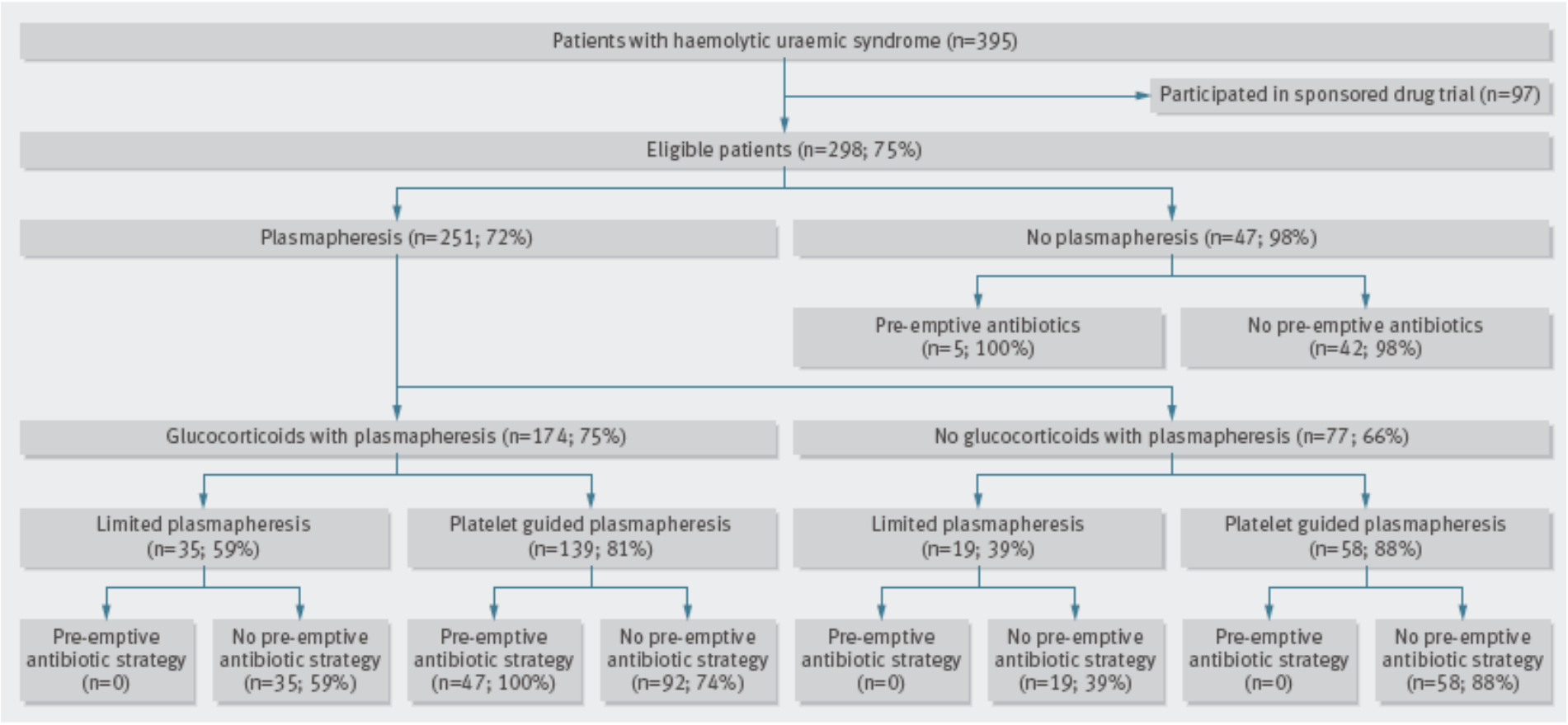
Expérience suite à épidémie 2011 DE,

Mais pas de RCT

Dundas. Lancet 2009
Michael. Cochrane Database Syst rev 2009
Colic. Lancet 2011
Kielstein. NDT 2012

Validation of treatment strategies for enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome: case-control study

Menne J. BMJ 2012.



SHU « atypique »

MAT

Micro**A**ngiopathies**T**hrombotiques

PTT

Purpura **T**hrombotique **T**hrombocytopénique

SHU

Syndrome **H**émolytique et **U**rémique

… mais nous allons voir que c'est un peu plus compliqué !

Hereditary TTP

Acquired TTP

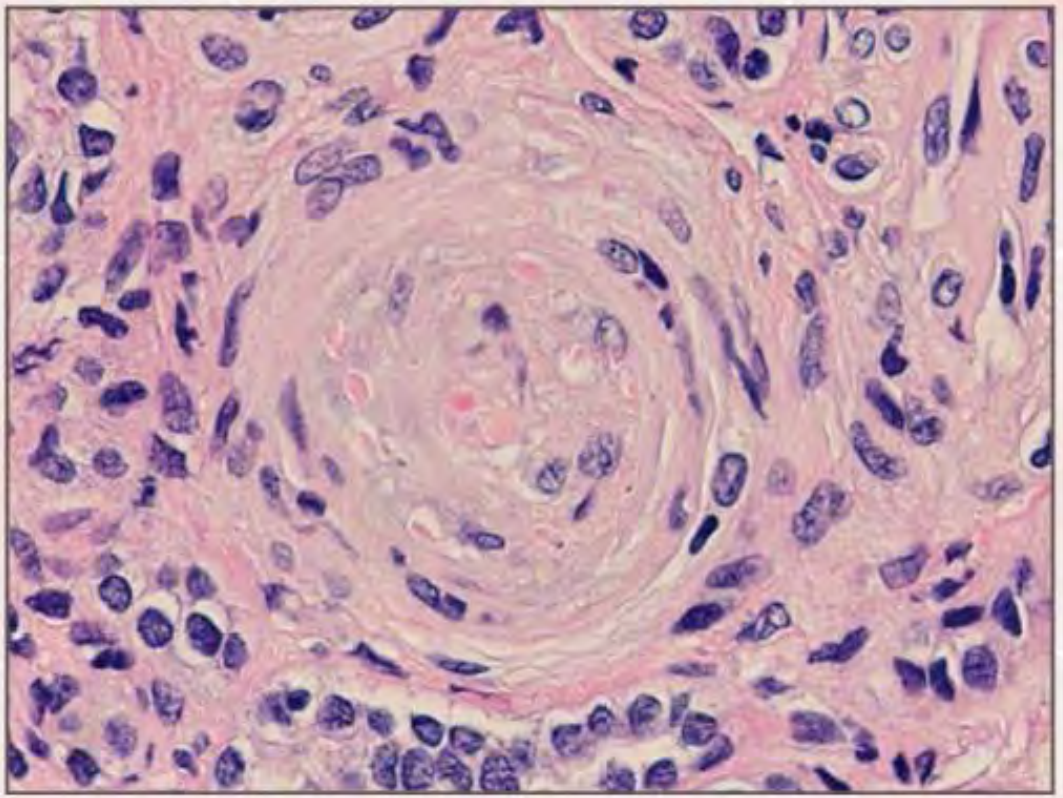
Coagulation-mediated TMA

CIVD
DGKE

Hereditary complement-mediated TMA

Acquired complement-mediated TMA

SHU atypique



Drug-mediated TMA (immune reaction)

Gemcitabine
Quinine

Drug-mediated TMA (toxic dose–related reaction)

Tacrolimus
VEGF inhib.

Metabolism-mediated TMA (cobalamin deficiency)

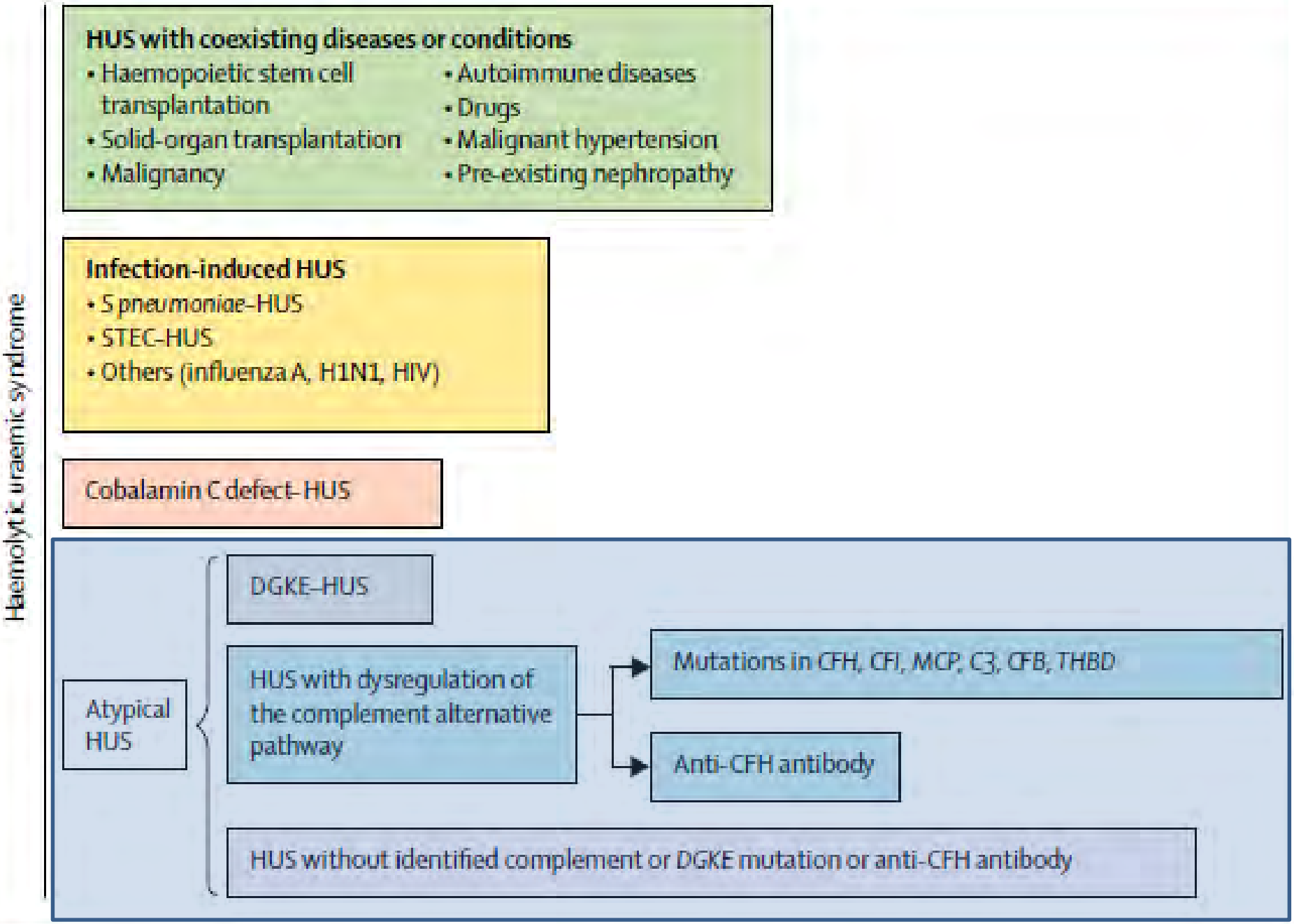
Georges et al. NEJM 2014

Autres pathologies peuvent associer anémie hémolytique et thrombopénie: DD!

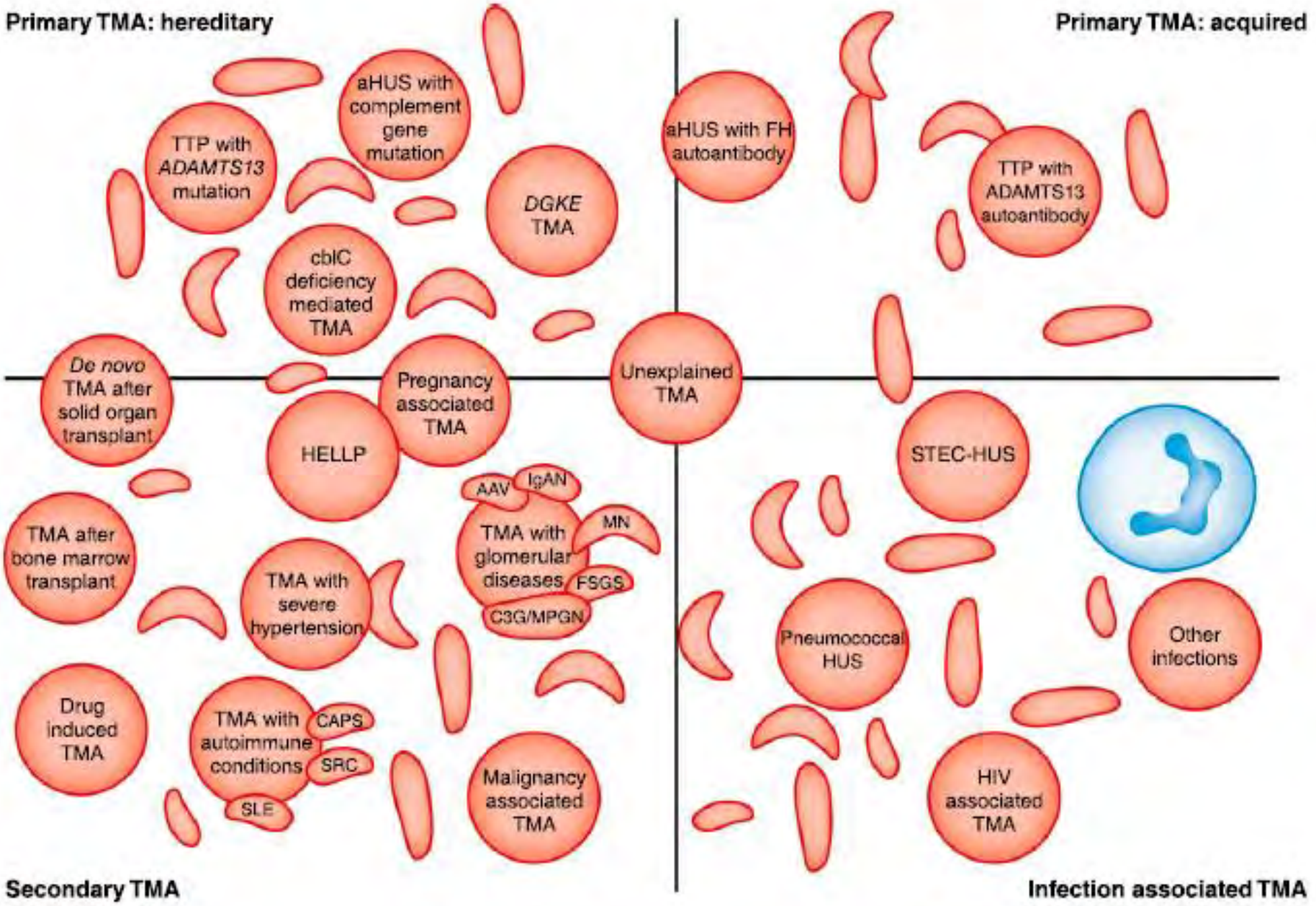
Systemic infection	Strep pneumoniae, H1N1, HIV, CMV, champignons
Systemic cancer	
Severe preeclampsia, eclampsia, HELLP syndrome	
Severe hypertension	
Autoimmune disorders (e.g., systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome)	
Hematopoietic stem-cell or organ transplantation	

! Une condition à risque peut révéler un SHU atypique (grossesse, transplantation…)

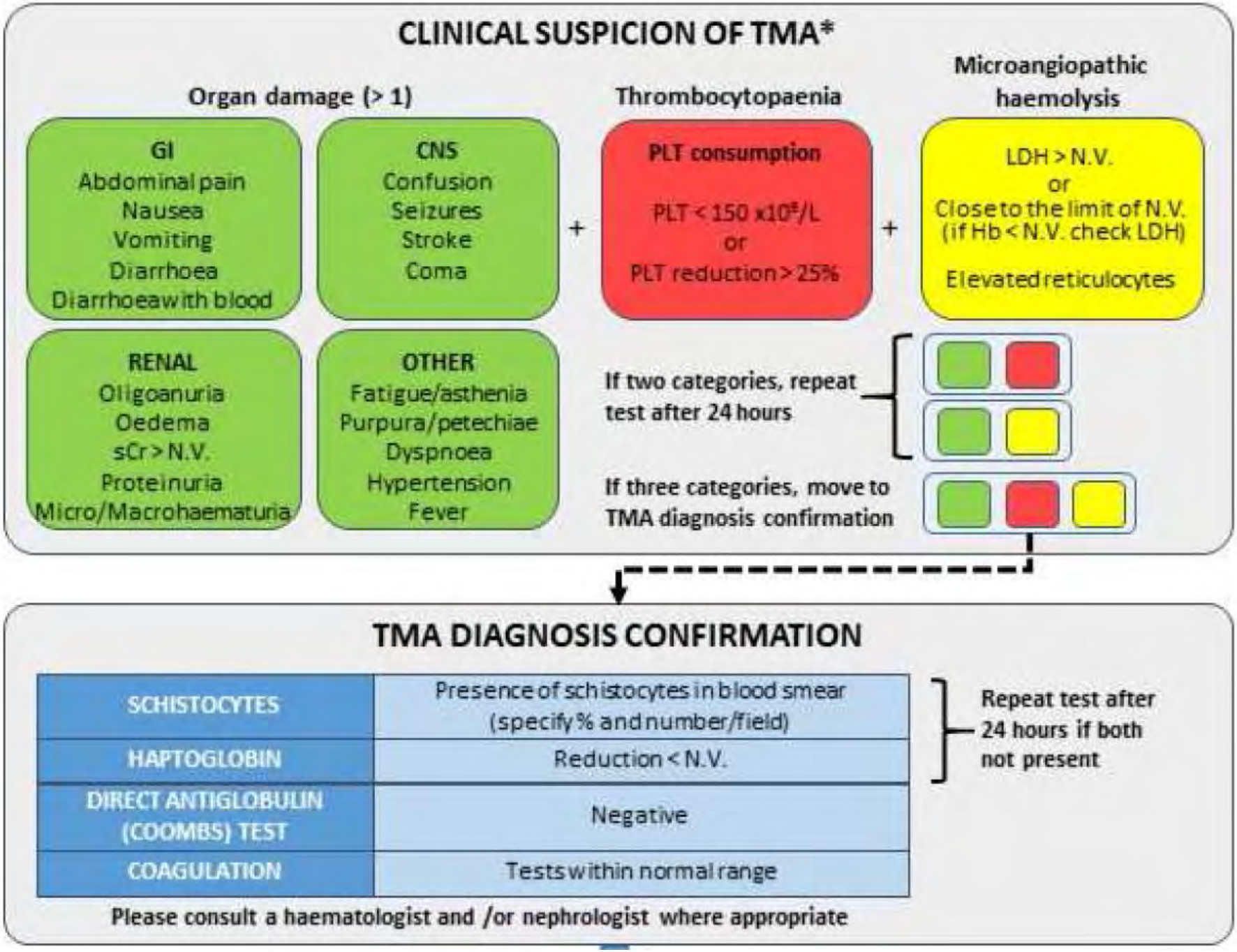
Georges et al. NEJM 2014
Masias. Blood 2017



Fakhouri. Lancet 2017



Brocklebank. CJASN2018



Azaya et al. Chest 2017

EXCLUDE OTHER CAUSES OF TMA

DIC: prothrombin time and aPTT prolonged; fibrinogen low (or low-normal with infection); D-dimers high; anti-thrombin and protein C low
Evans syndrome, S. pneumoniae HUS, Autoimmune hemolytic anaemia: Positive Coombs test
Drug use: heparin use, alcohol toxicity, ADP- receptor antagonists, GP IIb/IIIa inhibitors, calcineurin inhibitors, mitomycin C, quinine etc.
Disseminated malignancy/bone marrow carcinosis
Organ transplantation, including haematopoietic stem cell transplantation
Others**

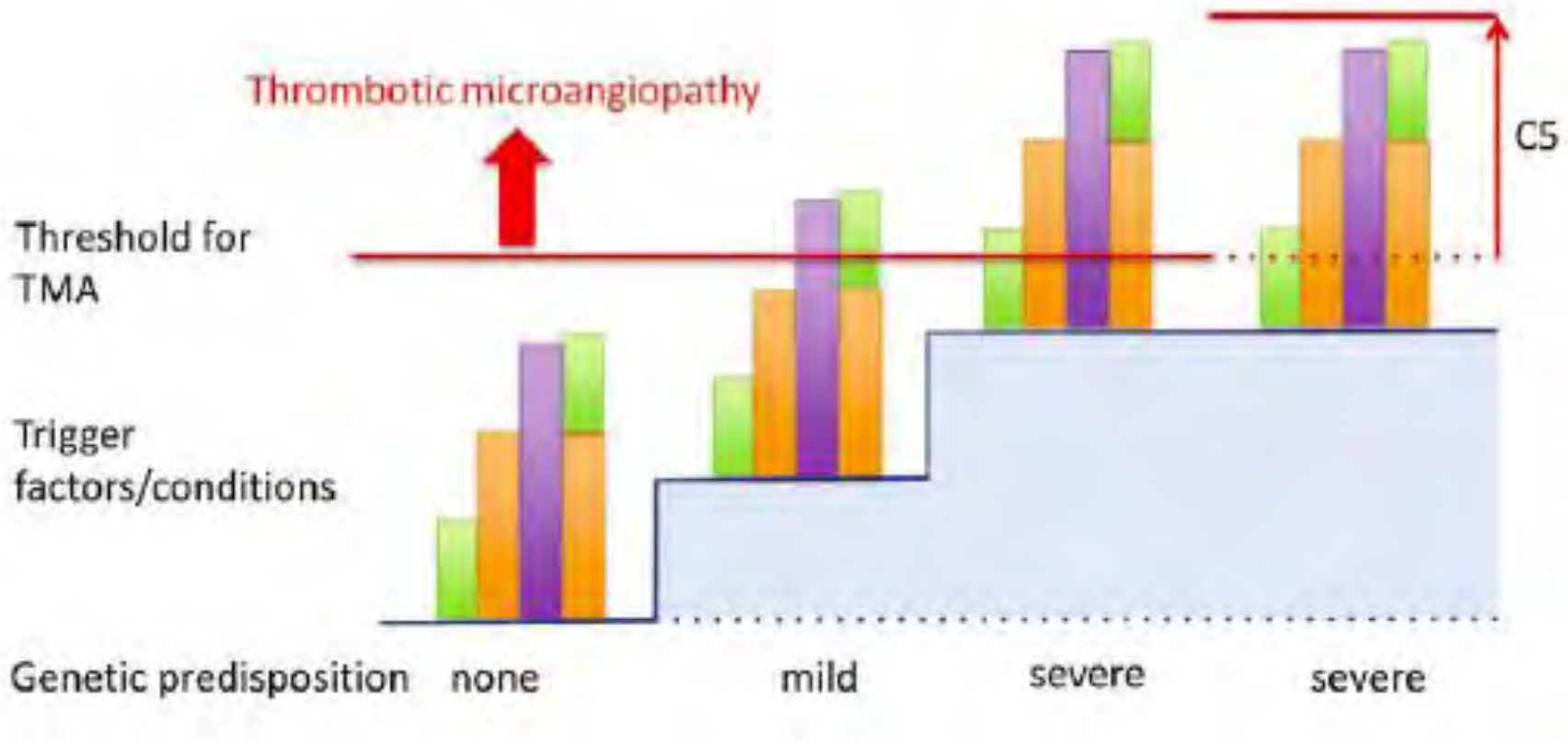
If symptoms persist after treatment of one of the above mentioned causes of TMA, consider differential diagnosis of aHUS, STEC-HUS or TTP

TMA DIFFERENTIAL DIAGNOSIS

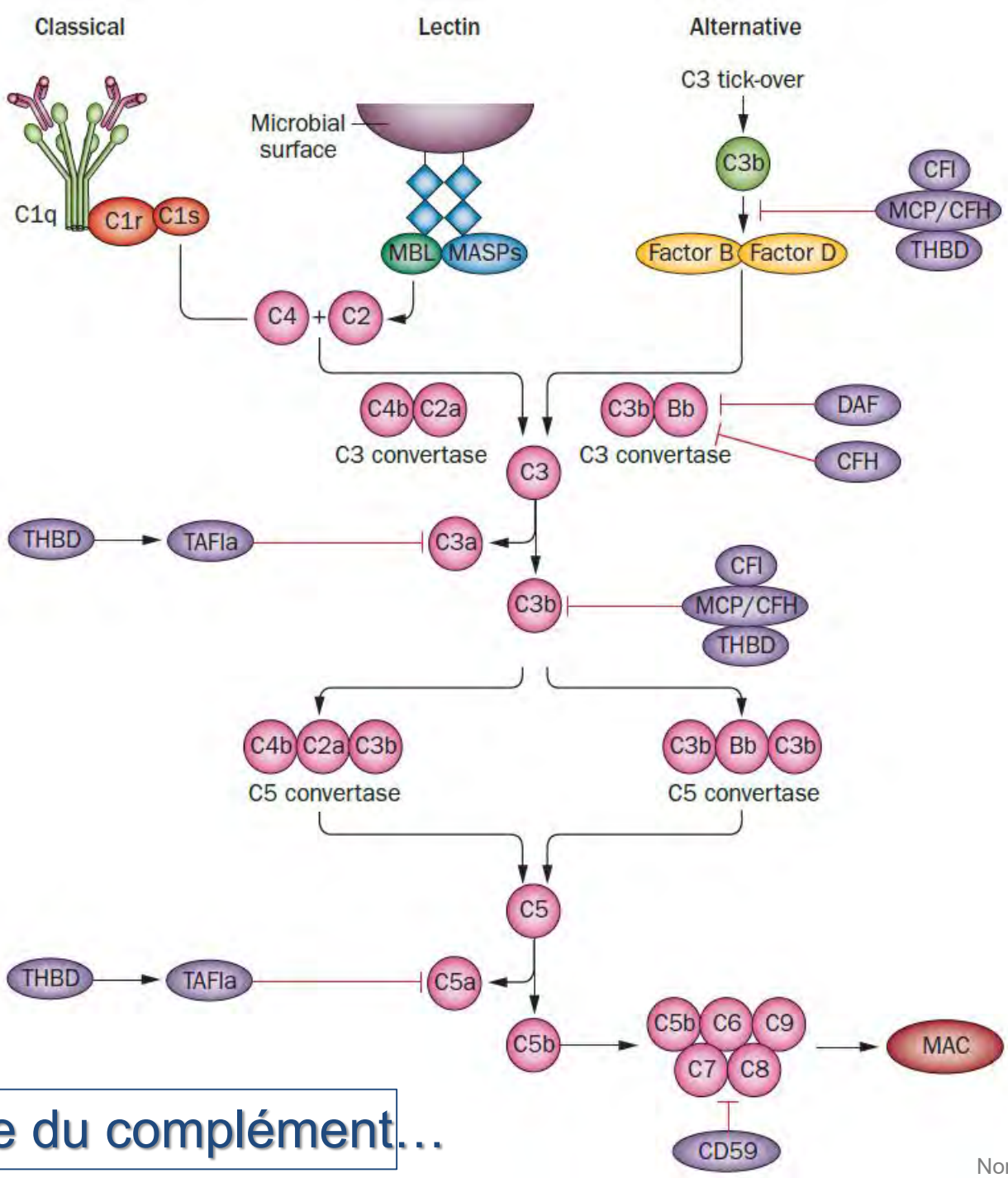
Family history of TMA and/or renal failure supports a diagnosis of aHUS or congenital TTP

Identify TMA		
Test	**Outcome in aHUS**	**In alternative diagnosis**
Reticulocyte counts	Increased	
Free serum haemoglobin	Increased	
LDH	Increased	
Haptoglobin	Decreased	Often decreased in TMAs, normal in DIC and sepsis
Schistocytes	Present	Can be present in all TMAs
Platelet count	Decreased (most of the time)	Can be reduced in all TMAs
Haemoglobin	Decreased	Can be decreased in all TMAs
Serum creatinine	Increased (most of the time)	Can be increased in all TMAs
Haematuria and proteinuria	Present (most of the time)	Can be present in all TMAs
Kidney biopsy[a]	Often arteriolar and/or glomerular affected	intracapillary thrombosis if kidney
Additional tests to perform to advise on other possible causes of TMA		
Direct antiglobulin test (Coombs test)	Negative	Positive in autoimmune haemolytic anaemias, Evans syndrome and pneumococcal HUS
Fibrinogen	Normal	Reduced fibrinogen and elevated fibrinogen degradation products in DIC
aPTT, PT	Normal	Prolonged in DIC
Plasma coagulation tests	Normal	Reduced in DIC
D-dimer	Normal (can be elevated)	Elevated D-dimer in DIC or TMA
Liver enzyme levels	Normal (can be elevated if liver is involved)	Elevated in HELLP syndrome
Viral infections, including HIV, HBV, HCV, and H1N1	Can be a precipitant of aHUS	Known external precipitant of TMA
Pregnancy test (where appropriate)	Pregnancy-triggered TMA caused by aHUS usually presents in late pregnancy or post partum	Pregnancy-triggered TMA caused by TTP usually presents during pregnancy
Antibody testing, including antinuclear antibody, lupus anticoagulant, antiphospholipid antibodies	Negative	Positive in systemic diseases like SLE, CAPS; 30% of TTP have positive ANA
Rule out TTP and STEC-HUS		
STEC infection: faecal sample or rectal swab test **for *E. coli*** and/or PCR for Shiga toxin, and serology of LPS of common Shiga toxin-producing strains	Negative	Positive in STEC-HUS
ADAMTS13	> 10% activity	< 10% activity in TTP

Prédisposition et facteurs favorisants

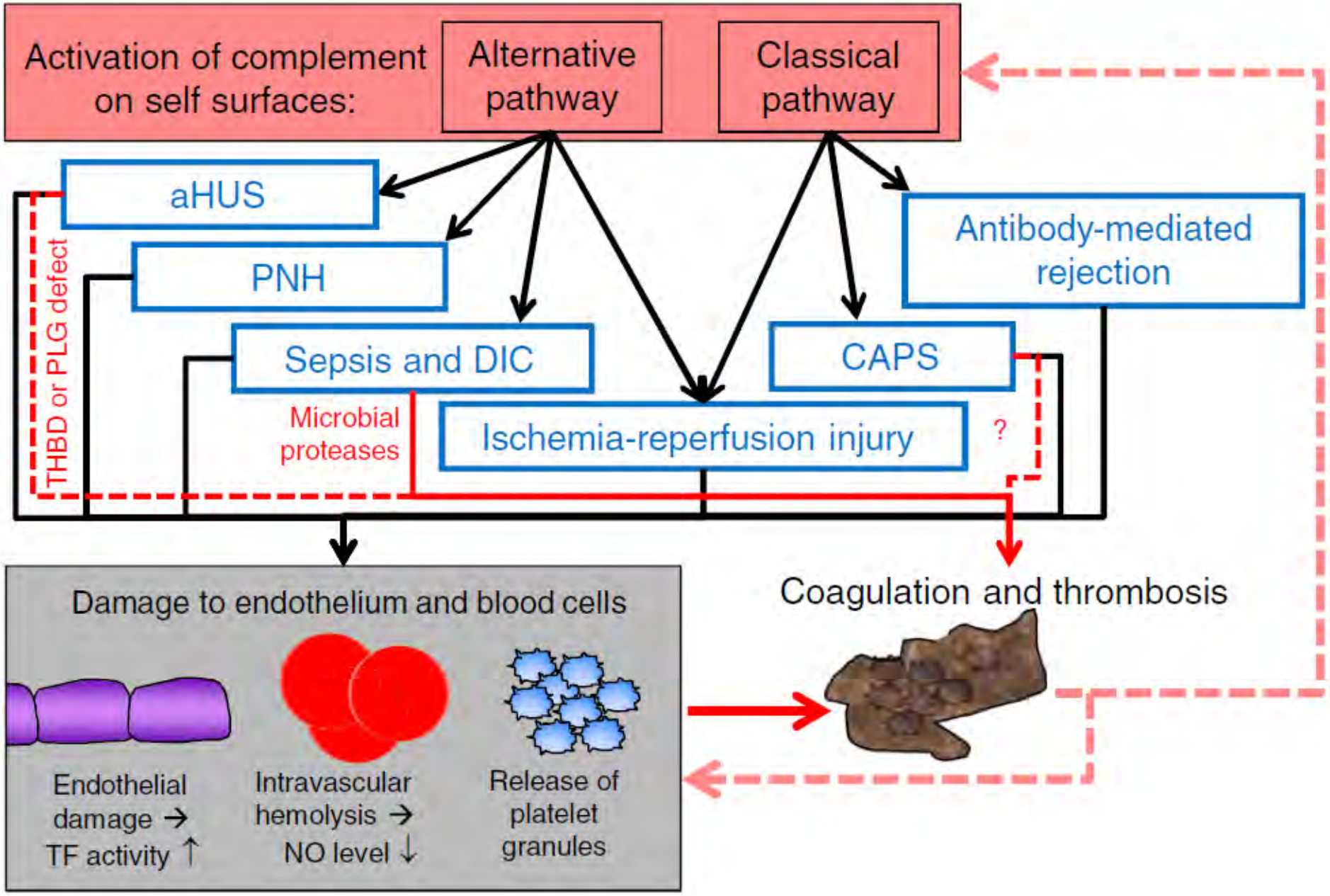


Riedl M, et al. *Semin Thromb Hemost* 2014

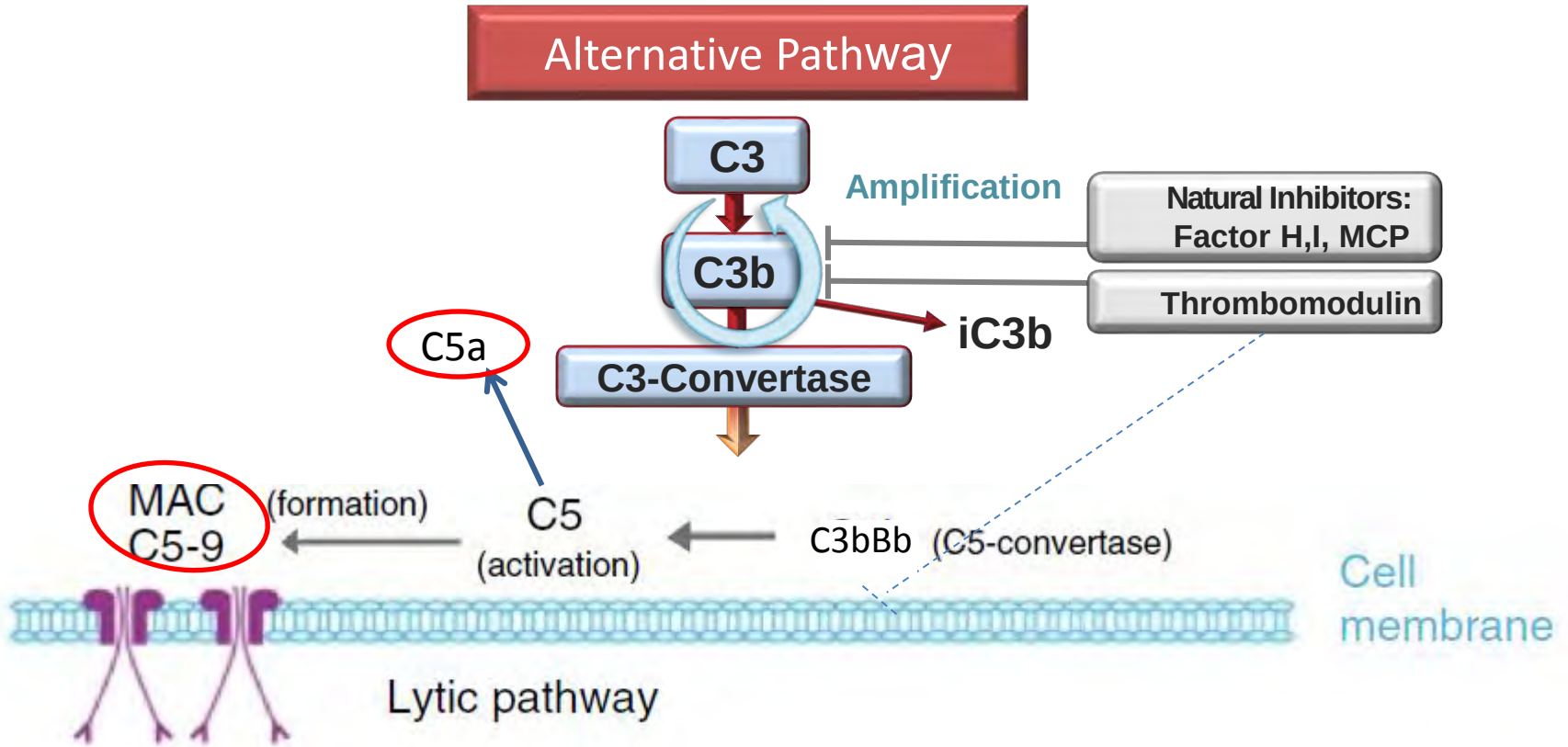


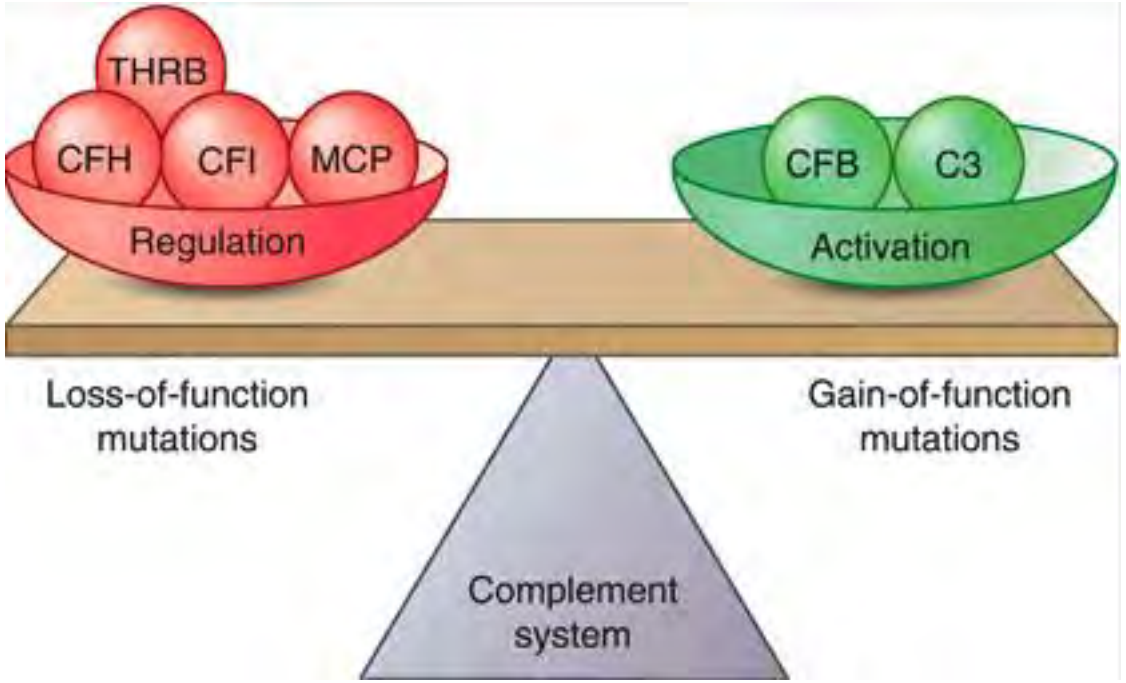
La cascade du complément…

Noris. Nat Nephrol Med 2012


Activation of complement on self surfaces:
Alternative pathway
Classical pathway
aHUS
PNH
Sepsis and DIC
Ischemia-reperfusion injury
CAPS
Antibody-mediated rejection
THBD or PLG defect
Microbial proteases
?
Damage to endothelium and blood cells
Endothelial damage → TF activity ↑
Intravascular hemolysis → NO level ↓
Release of platelet granules
Coagulation and thrombosis

aSHU: voie alterne du complément





Dans aSHU: 50-70% dysregulation voie alterne du complément

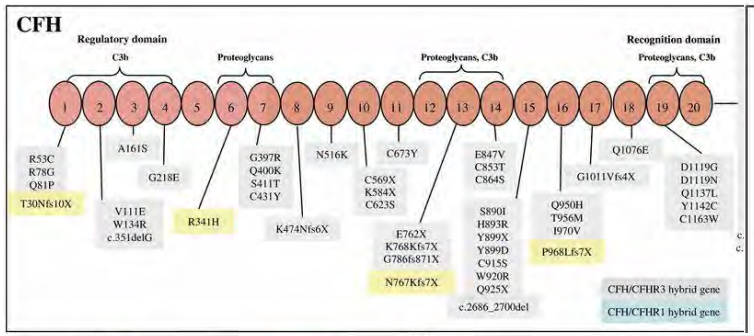
Mutated gene/protein	Type	Frequency (%)*	Death or end-stage renal disease 3-10 y after onset (%)†
Factor H (including *CFH/CFHR1* hybrid genes)	Loss of complement regulation	24-28	70-80
MCP (CD46)	Loss of complement regulation	5-9‡	<20
Factor I	Loss of complement regulation	4-8	60-70
C3	Gain of complement activation	2-8	60-70
Factor B	Gain of complement activation	0-4	70
Thrombomodulin	Possibly loss of complement regulation and procoagulative state	0-5	50-60
CFHR1/3 deficiency with anti-factor H autoantibodies	Loss of complement regulation	3-10§	30-70
Diacylglycerol kinase ε	Prothrombotic	0-3‖	46
None identified		30-48	50

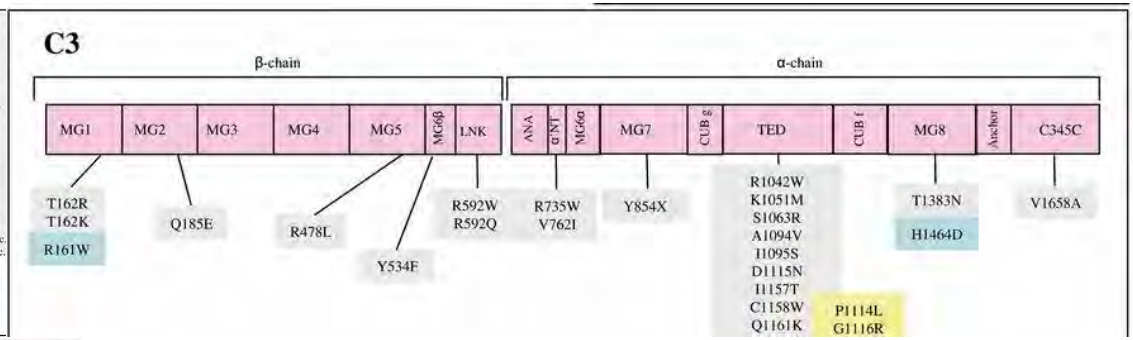
Goicoechea de Jorge E, et al. *Kidney Int.* 2010; Jokirante. Blood 2017

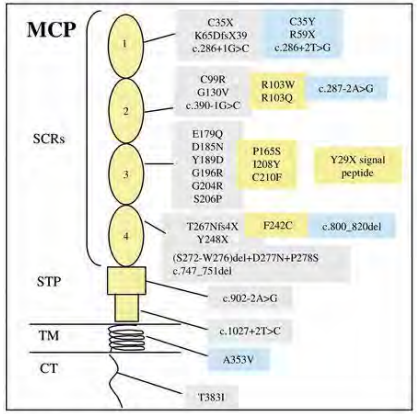
Examen initial: complément et activité des facteurs

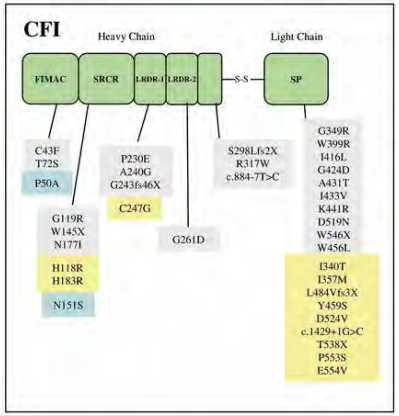
CH50 (%)	C3 (%)	C4 (%)	Interprétation	Examens complémentaires
Normal	Normal	Normal	Normal	Aucun
Augmenté	Augmenté	Augmenté	Syndrome inflammatoire	Aucun
Abaissé	Abaissé	Abaissé	Consommation par la voie classique ± de la voie alterne, Insuffisance hépatocellulaire, Fuite protéique	FB
Abaissé	Abaissé	Normal	Consommation voie alterne	FB, FH, FI, CD46, anticorps anti-FH,C3Nef (GPC3)
Normal	Normal	Abaissé	Déficit en C1 Inh Déficit partiel en C4 Cryoglobulinémie	C1 inh Ag et fonction Phénotypage C4, Rech cryoglobuline,
Abaissé	Normal	Normal	Activation in vitro Déficit hétérozygote en C2	Contrôle avec respect du pré-analytique Etude génétique du gène de C2
Indosable	Normal	Normal	Déficit homozygote en une protéine de la voie classique et la voie terminale Traitement par anti-C5	Dosages antigéniques +/- fonctionnels

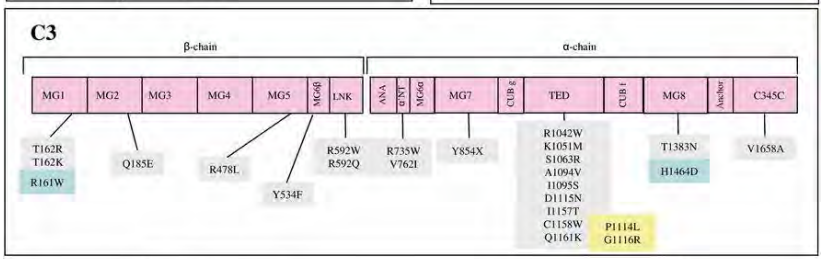
Recherche de mutations

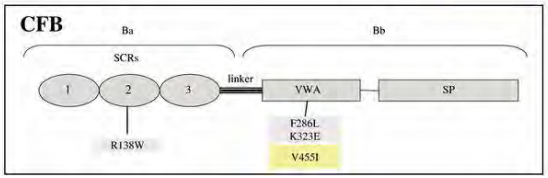












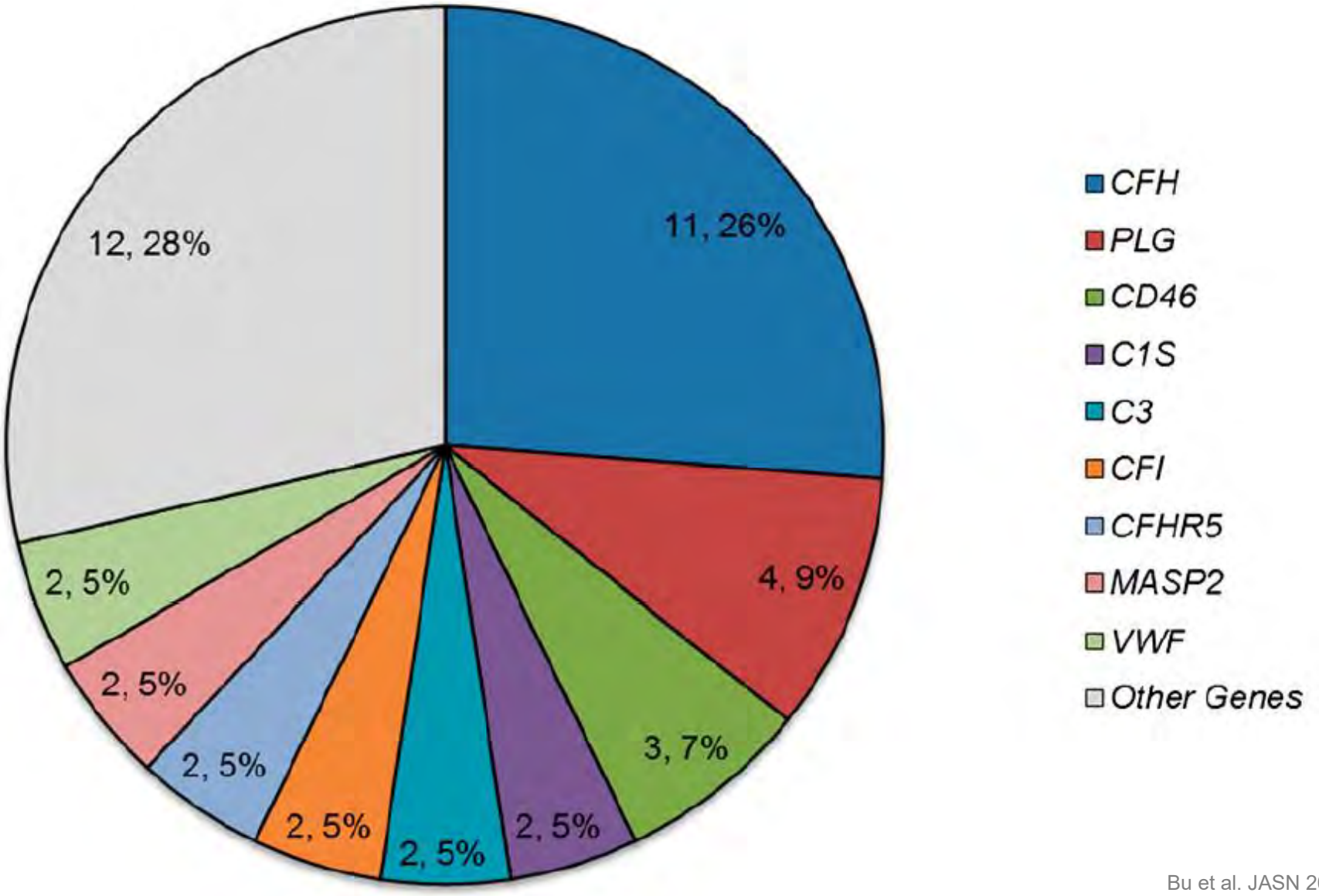
Localisation mutation CFH, MCP, CFI, C3 et CFB :

-27 patients ayant mutations combinées

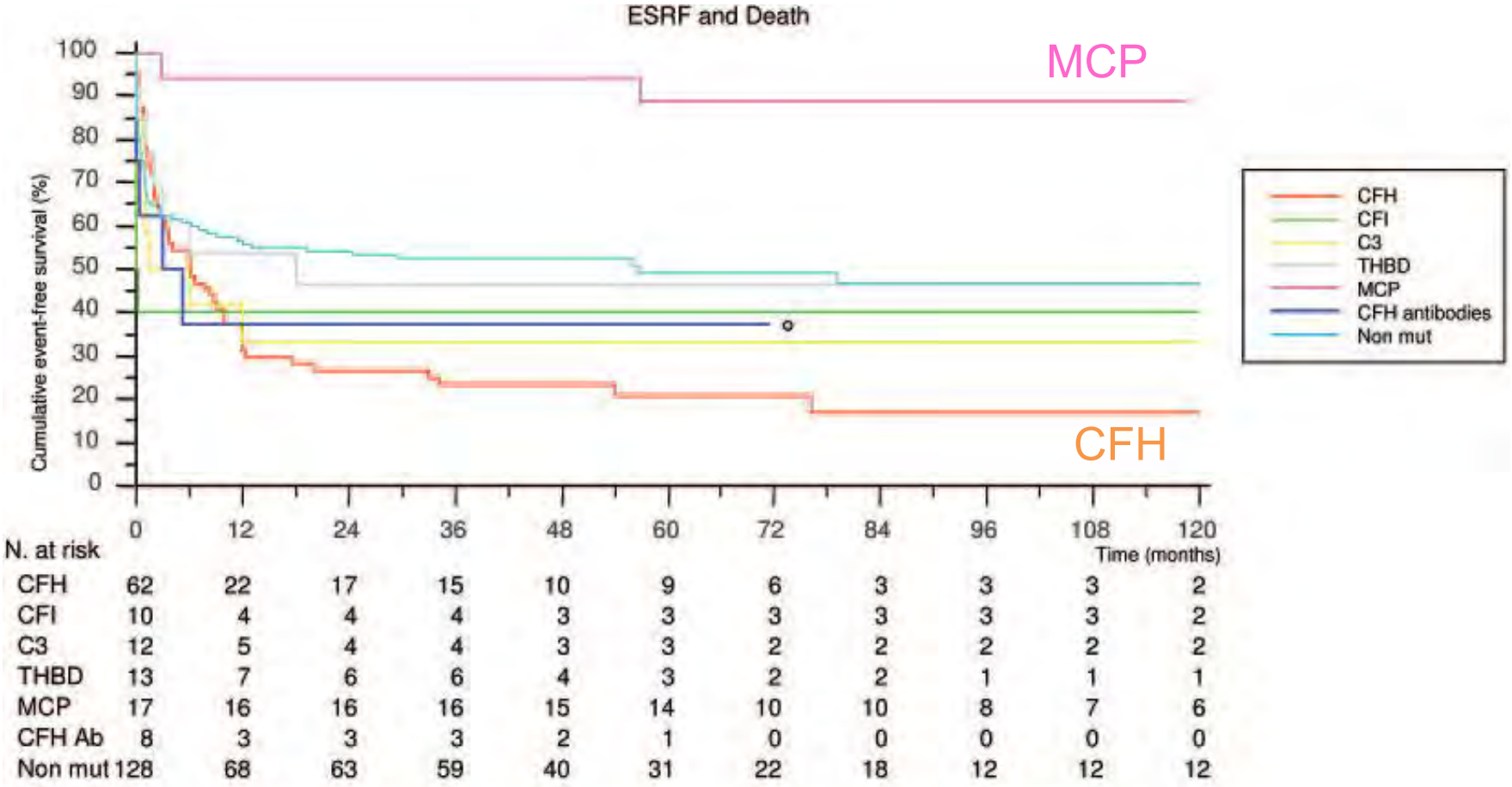
- patients issus de 4 cohortes avec 1 seule mutation

E Bresin et al. JASN 2013

Prévalence des mutations



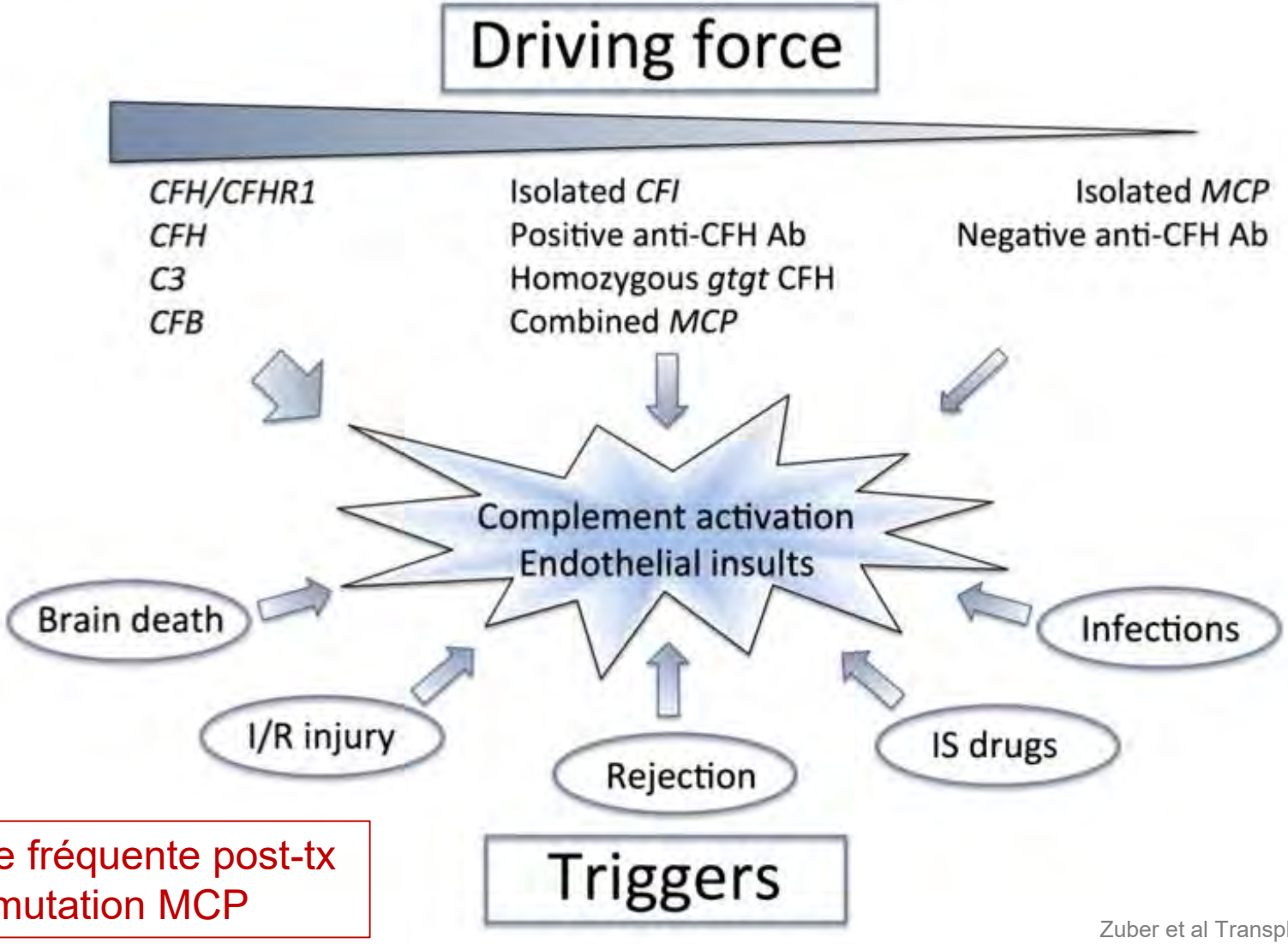
Bu et al. JASN 2014



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

Noris. CJASN 2010

Récidive post-transplantation rénale: Multi-hit paradigm



Récidive fréquente post-tx sauf si mutation MCP

Zuber et al Transplant Rev 2013

SHU atypique: Traitement

When must plasmatherapy be started?

- as soon as possible: within 24 hours after onset
- as soon as the patient's condition allows (blood pressure, volemia, hydroelectrolyte equilibrium, anemia corrected)

Which modality and which volume?

- PE: 1.5 plasma volume (60-75 ml/kg) with FFP for restitution
- if PE impossible, infuse FFP 10-20 ml/kg (if blood pressure and cardiac function are normal)

Which frequency during the first month?

- daily until stable nomalization of platelets, cessation of hemolysis and improvement renal function over several days. Consider administration of eculizumab if normalisation of platelet count, cessation of hemolysis and decrease of creatinine is not achieved after 3 to 5 daily PE.
- if initial plasmatherapy effective, complete 5 sessions per week during 2 weeks, followed by
- 3 sessions per week during up to 2 weeks

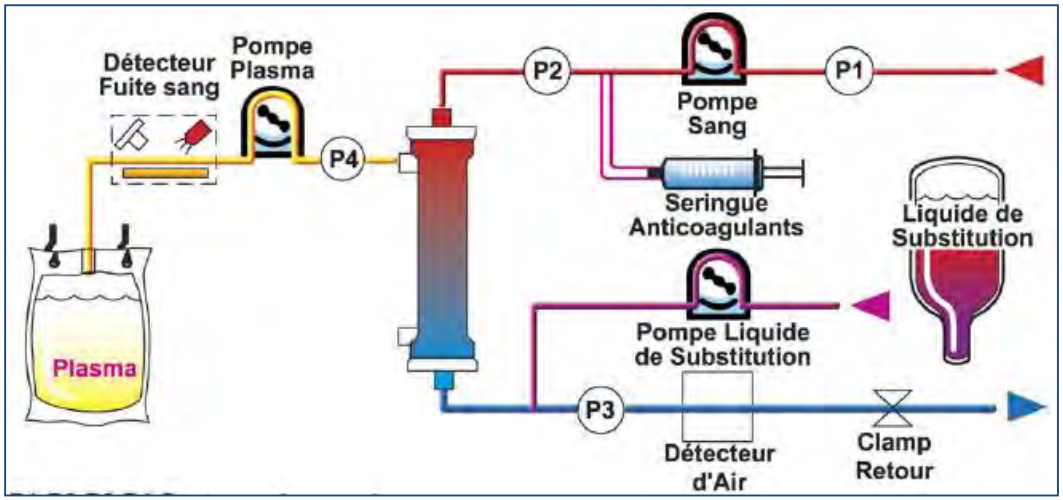
What are the situations which allow not to do PE or to stop early?

- MCP mutations (PE often performed during HUS episodes, with uncertain benefit, but not preventively)

Which frequency after the first month?

- empirical: determine the appropriate modality (PE or PI), threshold dose, interval between sessions and duration for each individual patient

✓Plasmaphérèse:



Rationnel→ enlève facteurs mutés
PFC apportent facteurs normaux

Pas d'étude clinique prospective
Ttt empirique

Ariceta et al. Ped Nephrol 2009
Taylor et al. B J Hematol 2010
Loirat. Presse Med 2012

aSHU: Plasmaphérèse

	Remission	Renal recovery	Death or ESRD at 3 years
CFH	63%	5%	77%
CFI	25%	12%	60%
C3	57%	43%	67%
THBD	88%	62%	54%
CFH Ab	75%	---	63%
CD46	97%	---	6%

Registre international italien (n=273) de 1996-2007

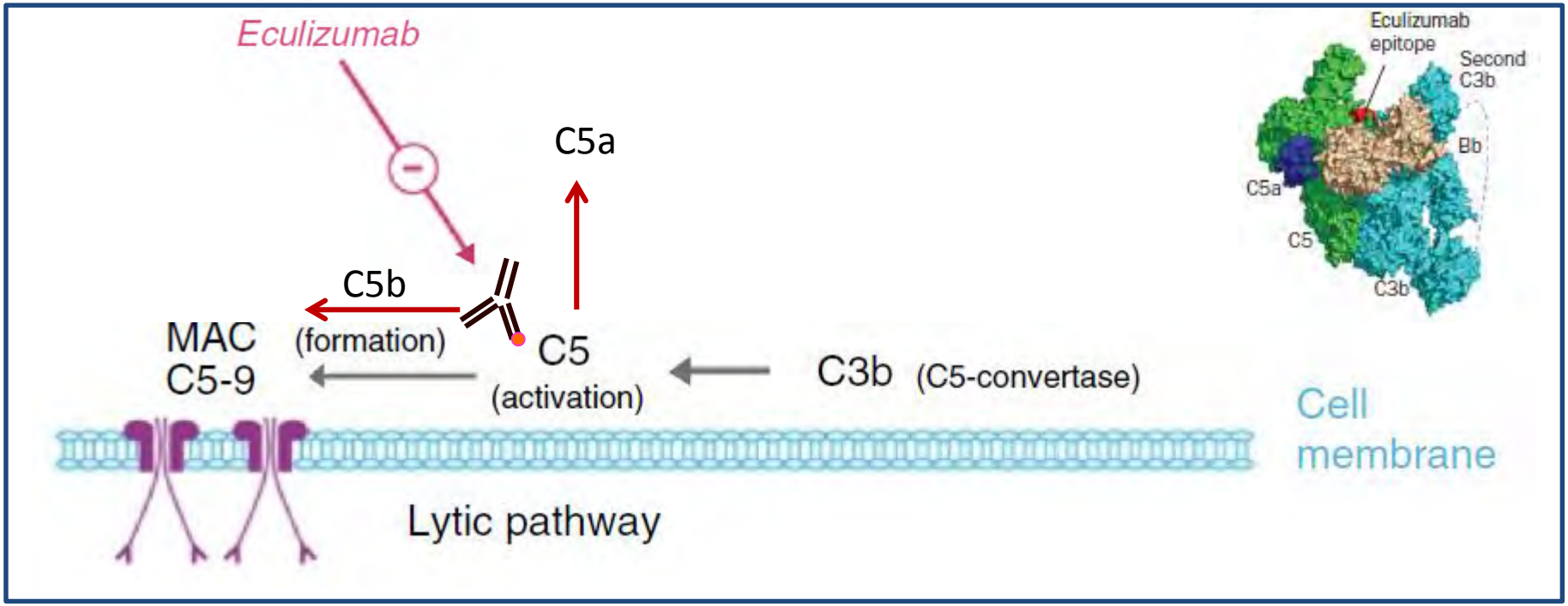
Pex entraine rémission 55-80% épisodes (= infusion plasma)
CFI – bon répondeur.

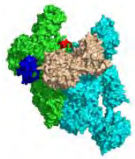
Problème: comment poursuivre sur long terme?

Noris CJASN 2010

aSHU: Eculizumab

Ac monoclonal humain hybrid IgG2/IgG4
Lie C5 et entraine donc un déficit fonctionnel en C5→ CH50 ↓





Eculizumab: pratique

Pediatric patients

- 5 kg to <10 kg: Induction with 300 mg weekly for one dose; maintenance 300 mg at week 2, then 300 mg every 3 weeks
- 10 kg to <20 kg: Induction with 600 mg weekly for one dose; maintenance 300 mg at week 2, then 300 mg every 2 weeks
- 20 kg to <30 kg: Induction with 600 mg weekly for two doses; maintenance 600 mg at week 3, then 600 mg every 2 weeks
- 30 kg to <40 kg: Induction with 600 mg weekly for two doses; maintenance: 900 mg at week 3, then 900 mg every 2 weeks
- ≥40 kg: Induction with 900 mg weekly for four doses; maintenance 1200 mg at week 5, then 1200 mg every 2 weeks

Adult patients

- Induction with 900 mg weekly for four doses; maintenance 1200 mg at week 5, then 1200 mg every 2 weeks

Risque de N Meningitidis
→ vaccination en prophylaxie ou ttt

Eculizumab: Practical Considerations
Before administration
Meningococcal vaccination mandatory
Tetravalent ACWY conjugated vaccine + multicomponent serogroup B vaccine
Prophylaxis
Long-term antibiotic prophylaxis recommended
Administration
Intravenous infusion
Maintenance therapy is administered every 14 d
Monitoring
CH50 and AH50 <10%
Eculizumab trough level 100 μg/ml
Hematologic indicators of TMA
Patient education
Vigilance regarding meningococcal infection
Counseling family members
Genetic screening
When to stop?
Continue during intercurrent illness, unless infection with encapsulated organism, due to high risk of TMA relapse in this context
Withdrawal
Systematic investigation in clinical trials is being undertaken
May be appropriate in some patients[a], with monitoring: liaise with specialist center

- Depuis 2009:
  - Utilisé off-label dans aSHU
  - Reins natifs et transplantation
  - Adultes and enfants
- En 2011:
  - Approbabtion de la FDA and European regulatory agencies en 1ère ligne pour aSHU

Pas d'ajustement de dose selon fonction rénale ou hépatique

Ajustement dose selon poids (< 40kg)

Induction 1-4 doses, puis thérapie de maintenance /2sem

Study C08-003
Adult/adolescent
(N=20)

Legendre et al. NEJM 2013

Study C08-002
Adult/adolescent
(N=17)

Licht et al. KI 2015

Study C10-003
Paediatrics
(N=22)

Greenbaum et al. KI2016

Study C10-004
Adults
(N=41)

Fakhouri et al. AJKD 2016

Eculizumab jusqu'à quand?

aHUS patients treated for at least 6 months (3 months in children with MCP mutations)
Stabilization of renal function for > 3 months in adults
Normalisation of renal function (eGFR, proteinuria) in children

- Patients with no identified complement genes pathogenic variants → Consider eculizumab discontinuation.
- Patients with *MCP* pathogenic variants → Consider eculizumab discontinuation. Kidney biopsy may be helpful to assess infra-clinical renal damage.
- Patients with *CFH* pathogenic variants → Decision to discontinue or not eculizumab should take into account the high-risk of relapse after treatment discontinuation.
- Patients with anti-CFH antibodies → Consider eculizumab discontinuation if anti-CFH antibodies < 1000 AU/ml following immunosuppressive treatment*.

In all cases, close monitoring of patients using blood tests and urinary dipsticks is mandatory after eculizumab discontinuation for early detection and treatment of aHUS relapse

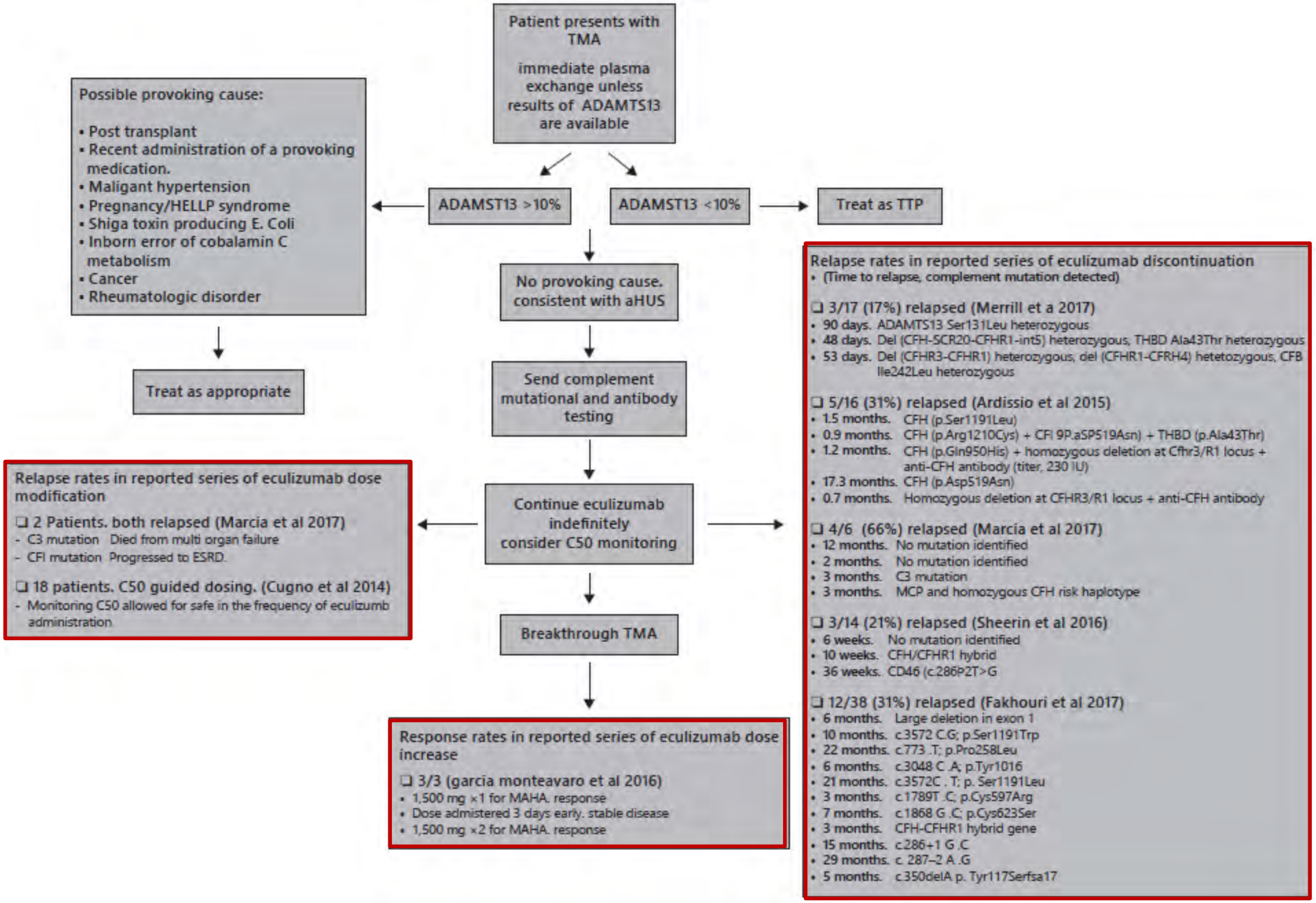
Patients who experience aHUS relapse after eculizumab discontinuation → « On-demand » treatment? Extended treatment?

ClinicalTrials.gov: NCT02574403

Fakhouri, cjasn 2017

Eculizumab : monitoring?

CH50 (Total complement activity)	**Description** • Measures the combined activity of all of the complement pathways • Tests the functional capability of serum complement components to lyse 50% of sheep erythrocytes in a reaction mixture • Will be low in congenital complement deficiency (C1–8) or during complement blockade • Normal range is assay dependent **Recommended goal during therapeutic complement blockade** • <10% of normal
AH50 (Alternative pathway hemolytic activity)	**Description** • Measures the combined activity of the alternative and terminal complement pathways • Tests the functional capability of alternate or terminal pathway complement components to lyse 50% of rabbit erythrocytes in a Mg^{2+}-EGTA buffer • Will be low in congenital C3, FI, FB, properdin, FH, and FD deficiencies or during terminal complement blockade • Normal range is assay dependent **Recommended goal during therapeutic complement blockade** • <10% of normal
Eculizumab trough	**Description** • May be a free or bound level • ELISA-based assay using C5 coated plates, patient sera, and an anti–human IgG detection system • Not affected by complement deficiencies **Recommended trough level during therapeutic complement blockade** • 50–100μg/ml
Alternative assays	**The following assays are under investigation (or awaiting to be replicated in different laboratories)[62] as a means to monitor therapeutic complement blockade** • Free C5 • *In vitro* human microvascular endothelial cell test[62] • sC5b-9 (also referred to as sMAC and TCC) may remain detectable in aHUS patients in remission and therefore is not recommended as a monitoring tool



Olson. Am J Nephrol 2018

EN RESUME…

Identifier la cause (PTT, ST-SHU, aSHU, SHU secondaire)

✓ Eviction médicaments, ttt cancer, ttt infection

✓ Plasmaphérèse avec PFC EN URGENCE

Indiquée dans PTT

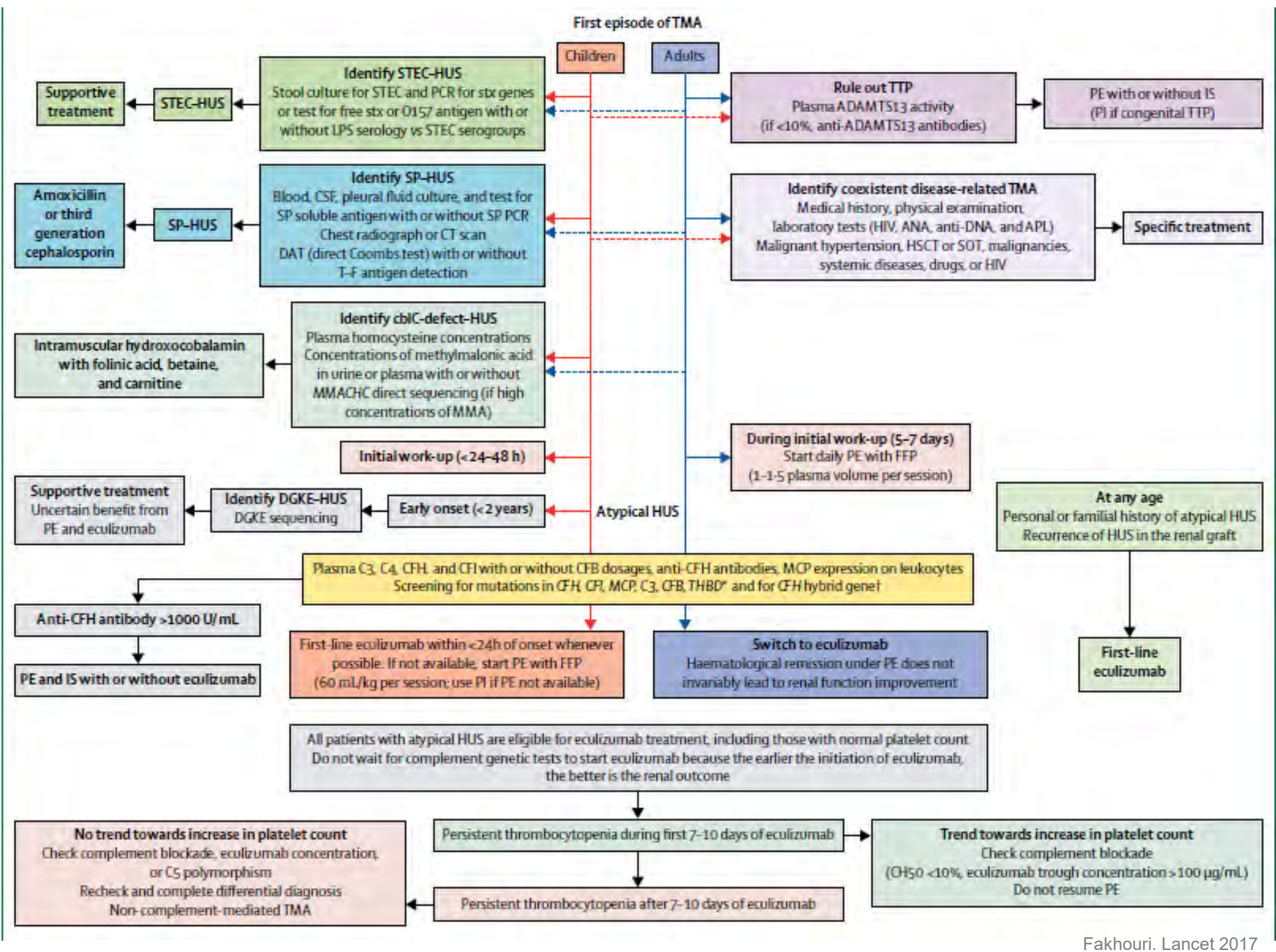
SHU atypique

Non indiquées dans causes secondaires (cancer, médicament)

Controversée dans St-SHU

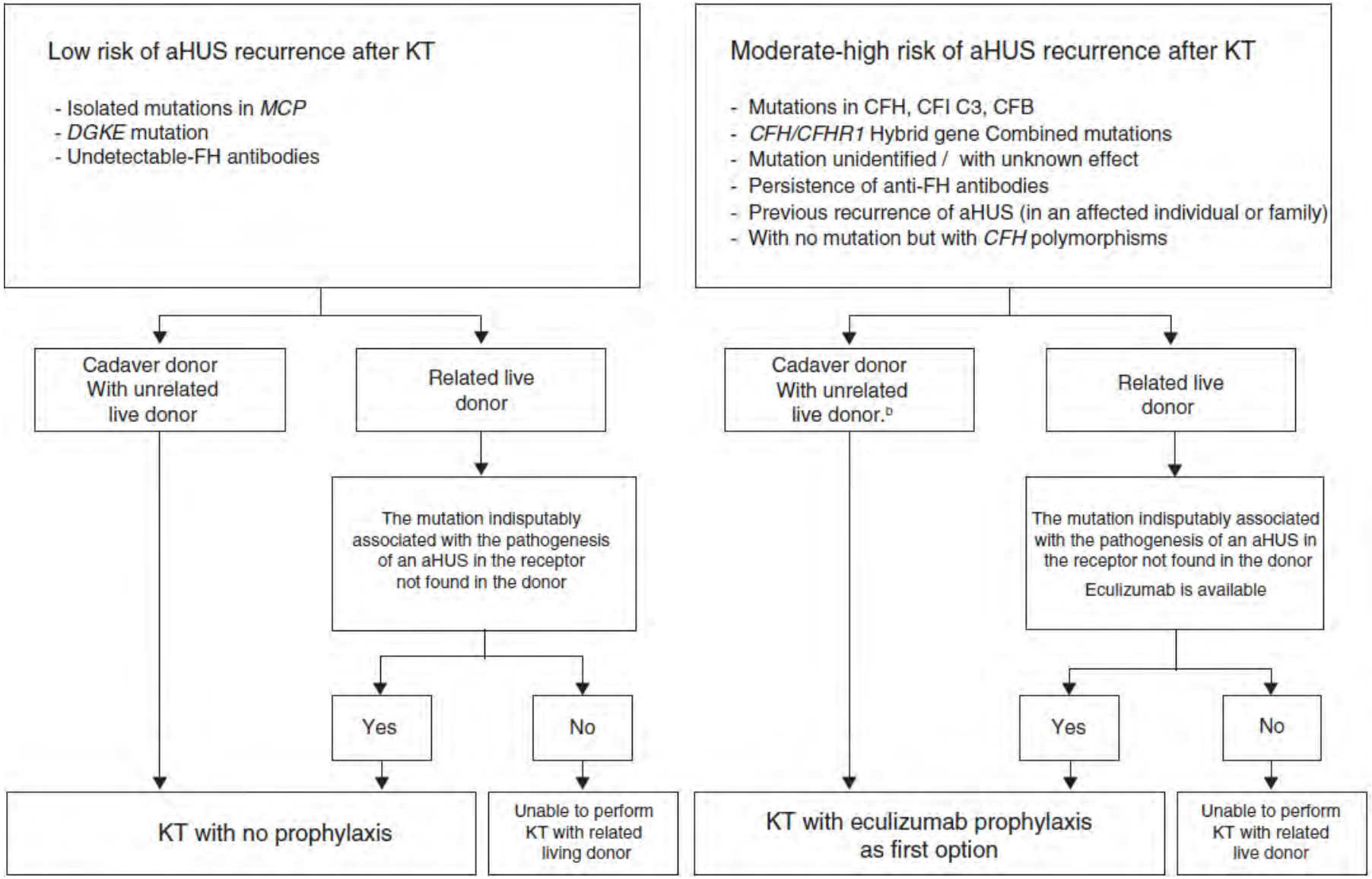
! Etude ADAMTS13 + activité complément + facteurs avant de débuter PEx. Après seule étude génétique possible.

✓Eculizumab à considérer dans SHU atypique



Fakhouri. Lancet 2017

Stratégie pour transplantation rénale…




THANK
YOU
GRACIAS
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EFCHARISTO
JUSPAXAR
DANKSCHEEN
TASHAKKUR ATU
YAQHANYELAY
SUKSAMA
EKHMET
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MERCI
BÏYAN
SHUKRIA
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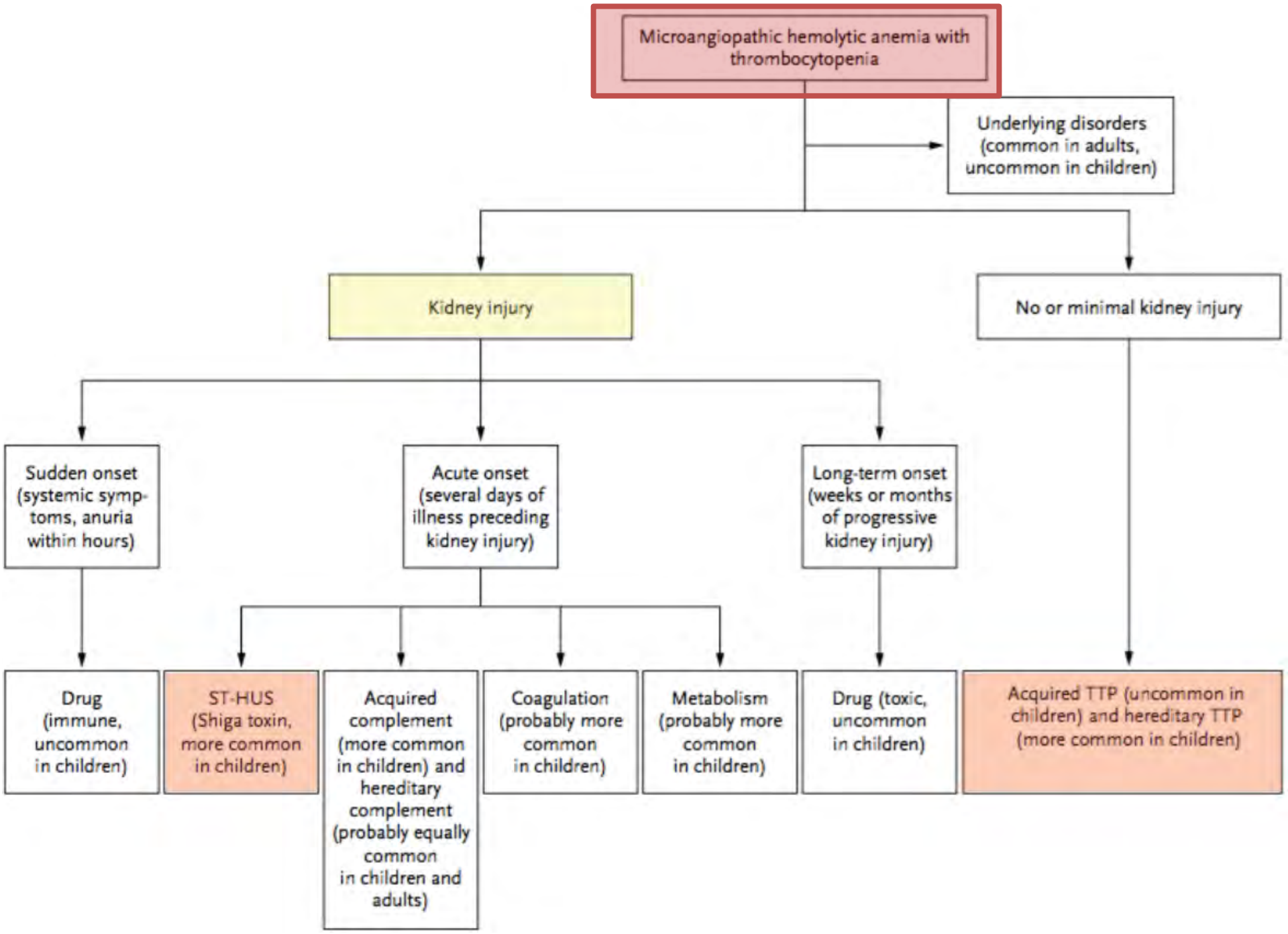
Microangiopathic hemolytic anemia with thrombocytopenia
Underlying disorders (common in adults, uncommon in children)
Kidney injury
No or minimal kidney injury
Sudden onset (systemic symptoms, anuria within hours)
Acute onset (several days of illness preceding kidney injury)
Long-term onset (weeks or months of progressive kidney injury)
Drug (immune, uncommon in children)
ST-HUS (Shiga toxin, more common in children)
Acquired complement (more common in children) and hereditary complement (probably equally common in children and adults)
Coagulation (probably more common in children)
Metabolism (probably more common in children)
Drug (toxic, uncommon in children)
Acquired TTP (uncommon in children) and hereditary TTP (more common in children)

Héréditaire…

Name	Cause	Clinical Features	Initial Management
Hereditary disorders			
ADAMTS13 deficiency–mediated TMA (also called TTP)	Homozygous or compound heterozygous *ADAMTS13* mutations	Initial presentation is typically in children but may also be in adults; possible evidence of ischemic organ injury; acute kidney injury is uncommon; patients with heterozygous mutations are asymptomatic.	Plasma infusion
Complement-mediated TMA	Mutations in *CFH, CFI, CFB, C3, CD46*, and other complement genes causing uncontrolled activation of the alternative pathway of complement	Initial presentation is often in children but may also be in adults; acute kidney injury is common; patients with heterozygous mutations may be symptomatic.	Plasma infusion or exchange, anti-complement agent
Metabolism-mediated TMA	Homozygous mutations in *MMACHC* (encoding methylmalonic aciduria and homocystinuria type C protein)	Initial presentation is typically in children <1 year of age; also reported in one young adult with hypertension and acute kidney injury.	Vitamin B_{12}, betaine, folinic acid
Coagulation-mediated TMA	Homozygous mutations in *DGKE;* mutations in *PLG* and *THBD* also implicated	Initial presentation with acute kidney injury is typically in children <1 year of age with *DGKE* mutations; clinical features of disorders associated with other mutations have not been described.	Plasma infusion

Georges et al. NEJM 2014

Acquis…

Acquired disorders			
ADAMTS13 deficiency–mediated TMA (also called TTP)	Autoantibody inhibition of ADAMTS13 activity	Initial presentation is uncommon in children; often presents with evidence of ischemic organ injury; acute kidney injury is uncommon.	Plasma exchange, immunosuppression
Shiga toxin–mediated TMA (also called ST-HUS)	Enteric infection with a Shiga toxin–secreting strain of *Escherichia coli* or *Shigella dysenteriae*	Initial presentation is more common in young children, typically with acute kidney injury; most cases are sporadic; large outbreaks also occur.	Supportive care
Drug-mediated TMA (immune reaction)	Quinine and possibly other drugs, with multiple cells affected by drug-dependent antibodies	Initial presentation is a sudden onset of severe systemic symptoms with anuric acute kidney injury.	Removal of drug, supportive care
Drug-mediated TMA (toxic dose–related reaction)	Multiple potential mechanisms (e.g., VEGF inhibition)	Gradual onset of renal failure occurs over weeks or months.	Removal of drug, supportive care
Complement-mediated TMA	Antibody inhibition of complement factor H activity	Initial presentation is acute kidney injury in children or adults.	Plasma exchange, immunosuppression, anticomplement agent

Georges et al. NEJM 2014

	Children			Adults				
	Pre-eculizumab era		Eculizumab	Pre-eculizumab era		Eculizumab		
	French cohort[2] (n=89)	Italian cohort[3] (n=149)	Trial 3[138,140] (n=22)	French Cohort[2] (n=89)	Italian cohort[3] (n=149)	Trial 1[141,142] (n=17)	Trial 2[141,142] (n=20)	Trial 4[143,144] (n=41)
First episode	16%	..	..	46%	..	..	..	..
6-month follow-up	..	..	9%	..	..	6%	10%	15%
1-year follow-up	29%	..	9%	56%	..	6%	10%	15%
2-year follow-up	..	..	..	..	..	12%	10%	..
3-year follow-up	..	48%	..	..	67%	..	..	..
5-year follow-up	36%	..	..	64%	..	..	..	..

For a detailed table legend see the appendix (pp 27, 28). HUS=haemolytic uraemic syndrome.

Table 2: Percentage of patients with atypical HUS who progressed to end-stage renal disease or who died in four prospective trials of eculizumab compared with the Italian and French registries of the pre-eculizumab era