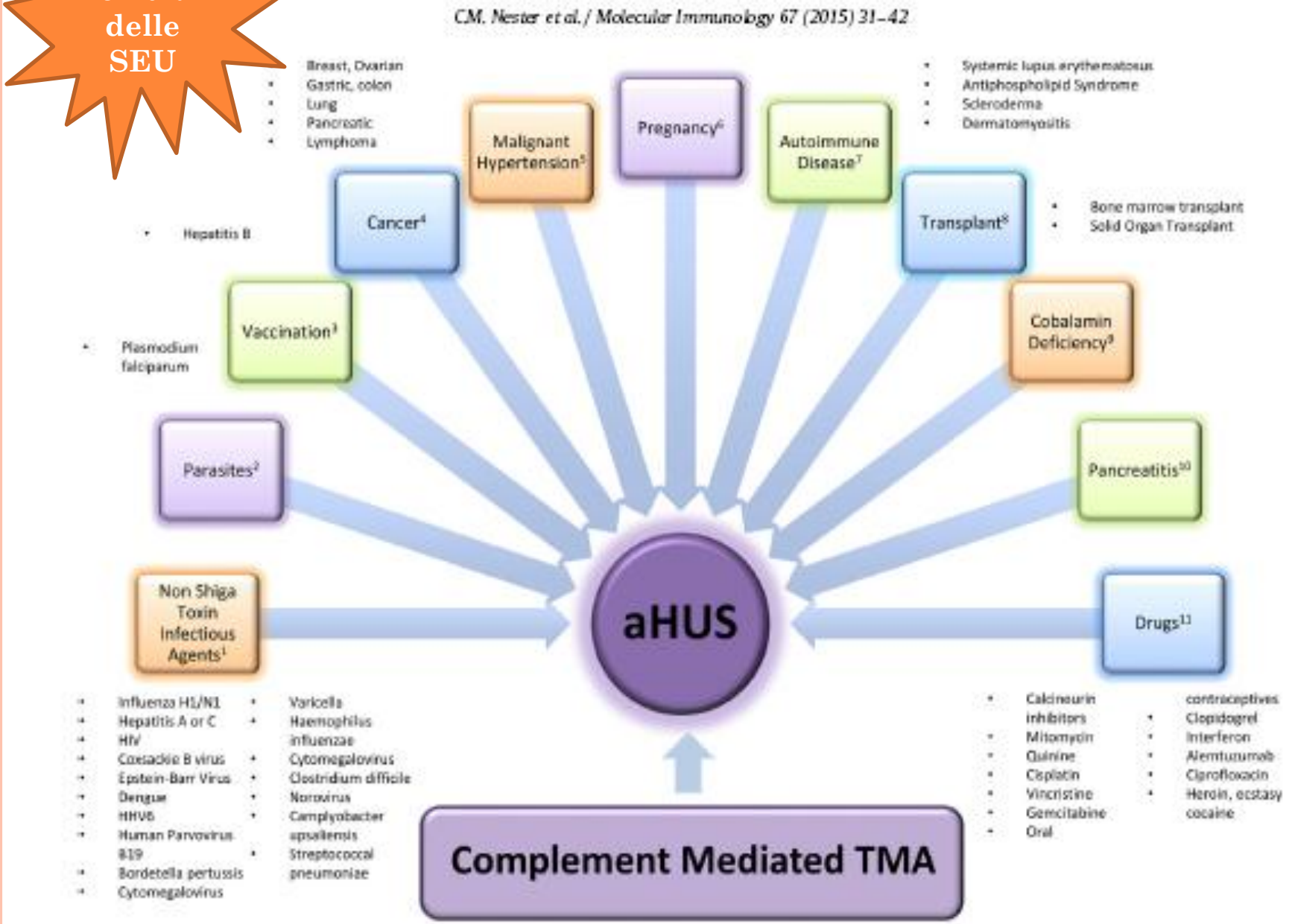
Azienda Ospedaliero Universitaria Careggi

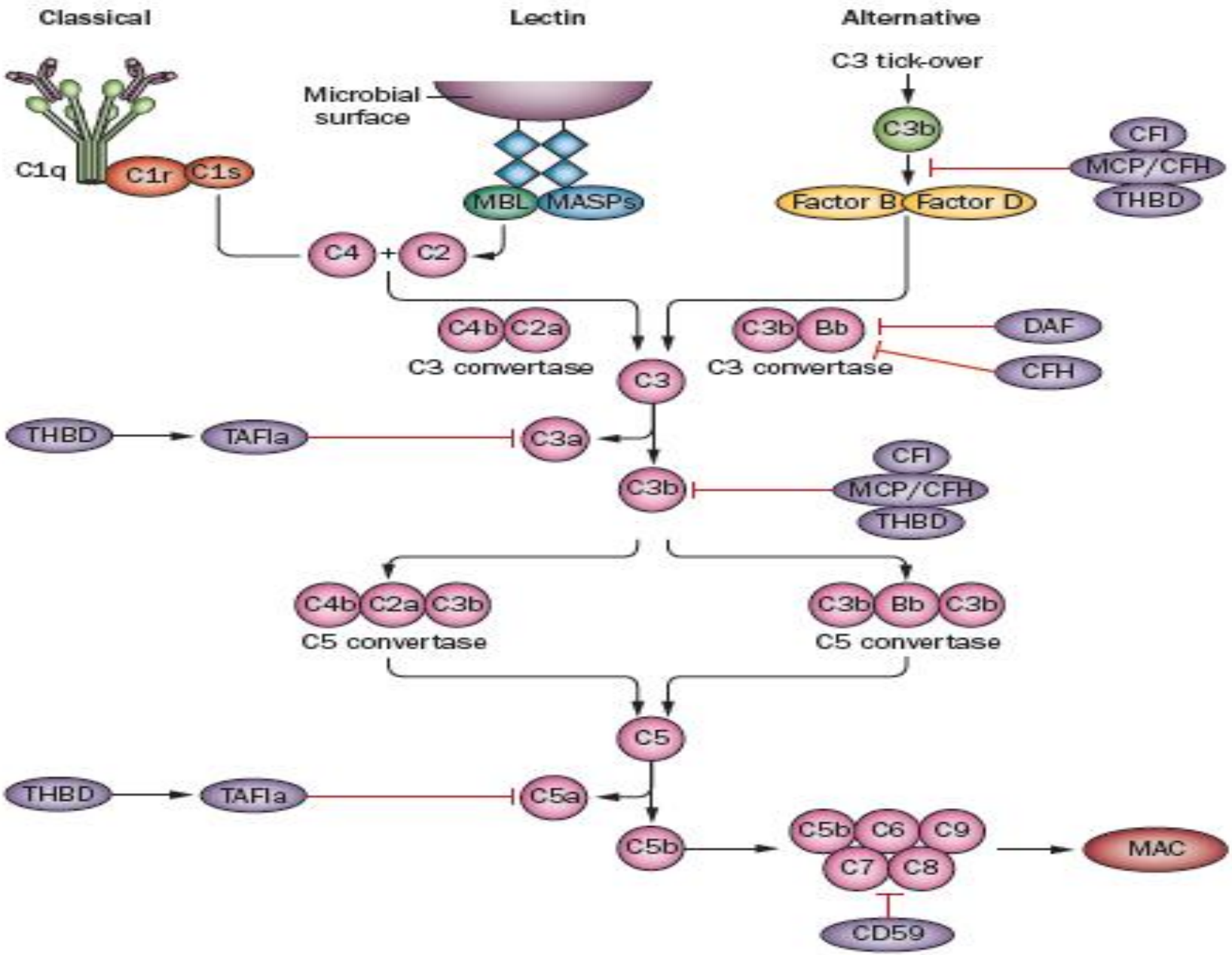
SEU ATIPICA: QUADRI CLINICI E TERAPIA NEFROLOGICA

Dott.ssa Giulia Antognoli
SOD Nefrologia e Dialisi
AOU Careggi Firenze

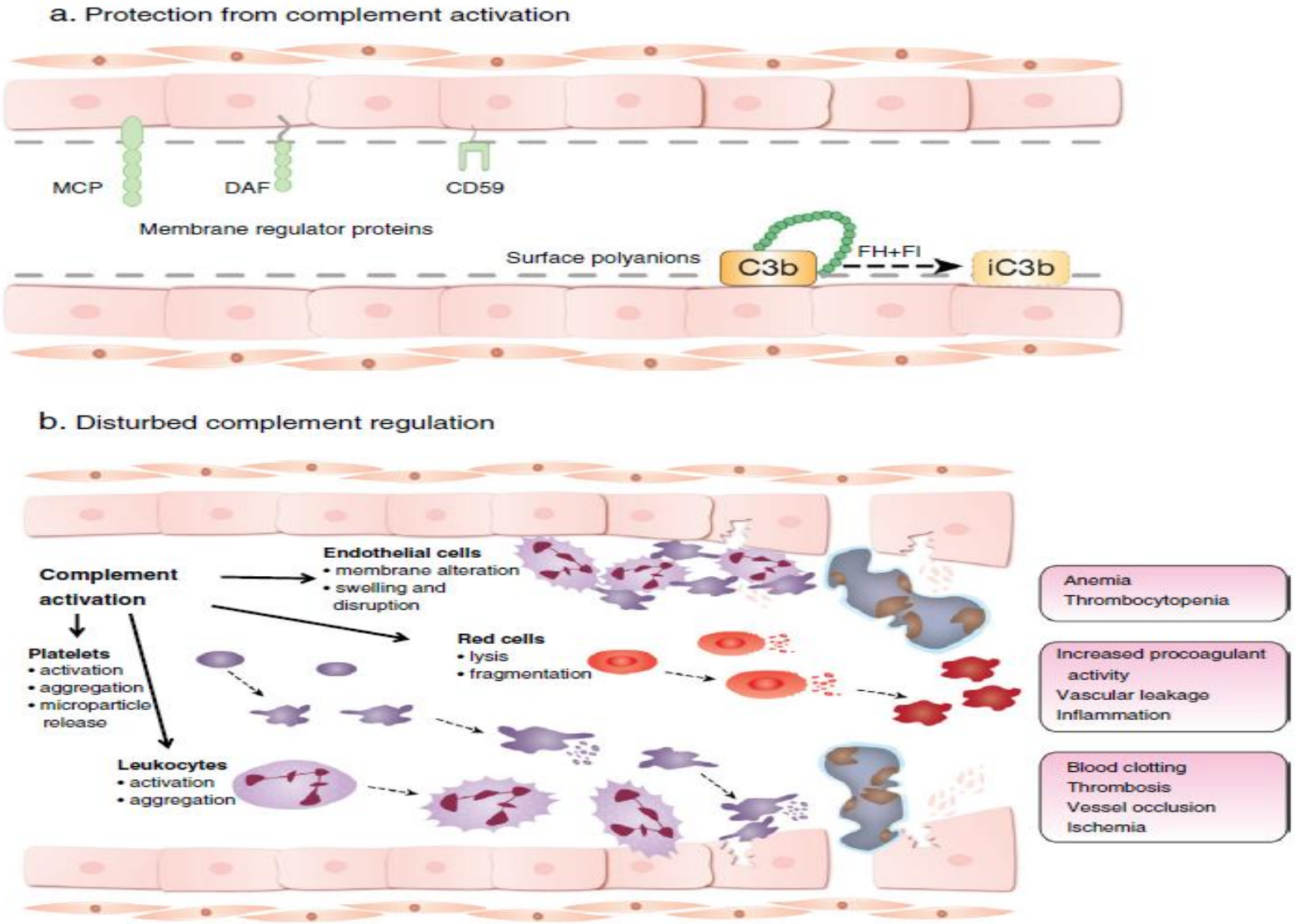
SST Servizio Sanitario della Toscana

5-10% delle SEU





Noris M *et all. Nat Rev Nephrol. 8, 622–633 (2012)*



European Journal of Internal Medicine 24 (2013) 496–502

Epidemiologia

- Incidenza 1-2 casi per milione di abitanti

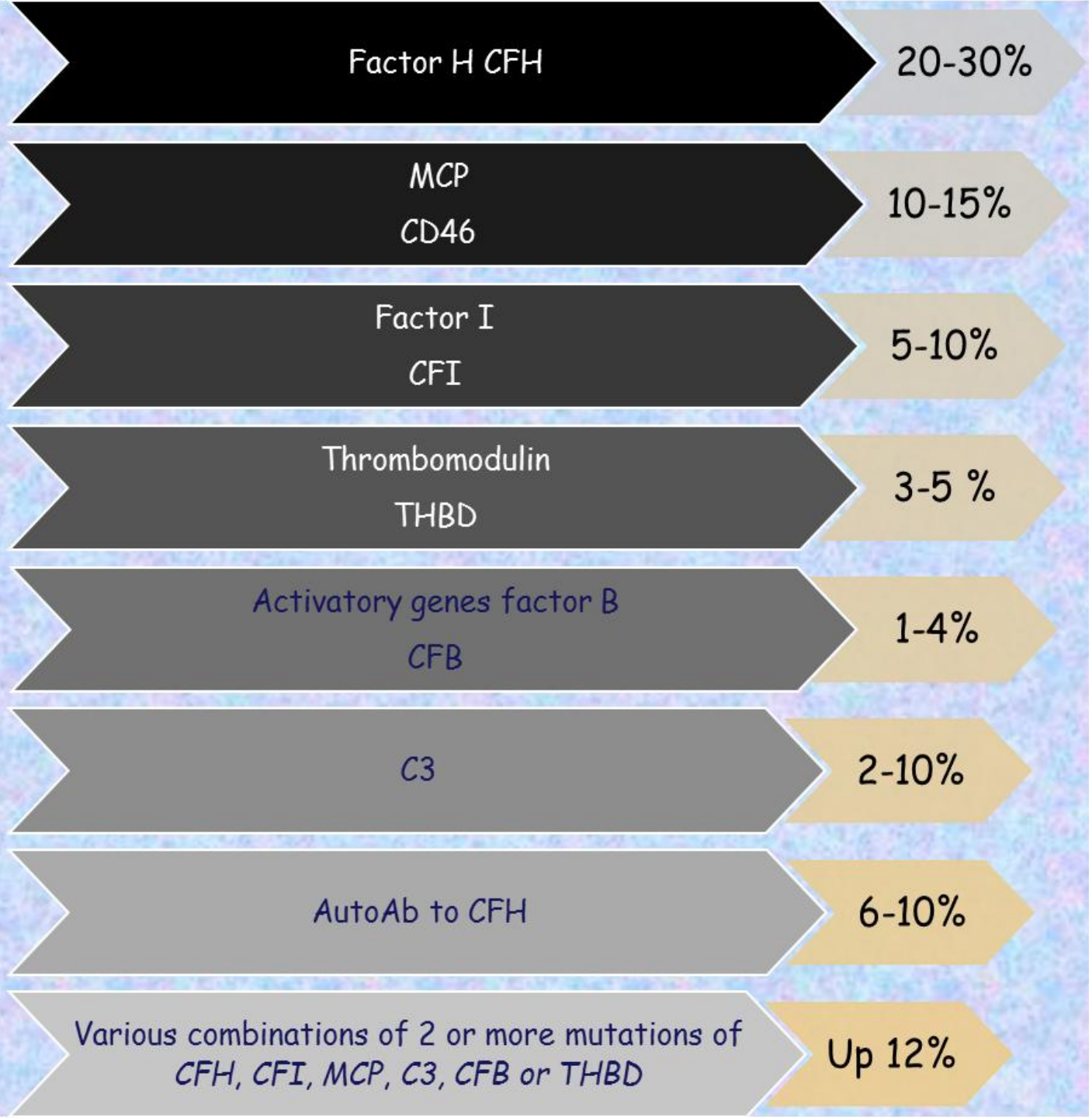
Noris M et all. N Eng J Med 2009; 361: 1676-87
Fremeaux Bacchi V et all. Clin J Am Soc Nephrol 2013; 8: 554-62

- 53-57% in età adulta

Licht C et all. BMC Nephrology 2015; 16:207

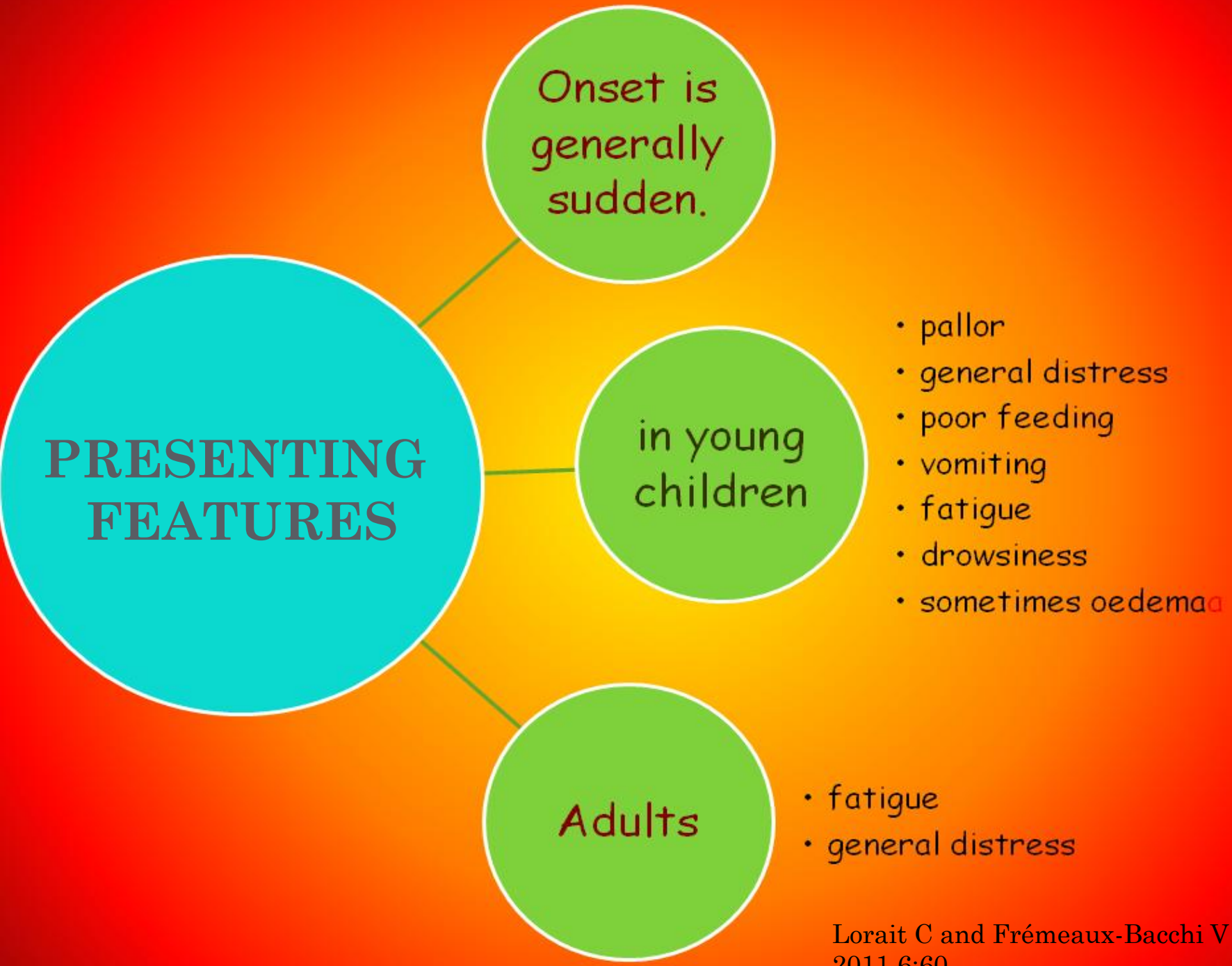
- F=M in età pediatrica
- F>M in età adulta

Sellier-Leclerc AL et al. J Am Soc Nephrol 2007; 18:2392-2400
Sullivan M et all. Ann Hum Genet 2010; 74:17-26



50-60% delle SEUa

Lorait C and Frémeaux-Bacchi V OJRD 2011,6:60



Lorait C and Frémeaux-Bacchi V OJRD 2011,6:60

Triade clinica

1. Piatrinopenia: plt < 150 x10^9/mm^3 o riduzione > 25% rispetto ai valori abituali

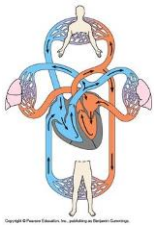
2. Anemia emolitica: Hb < 10 g/dl, ↑ LDH, ↑ bilirubina, ↓ aptoglobina, schistociti nel SP, Coombs neg

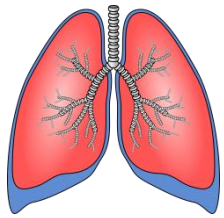
3. Insufficienza renale acuta ± oligo-anuria ± proteinuria

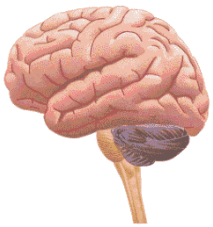
Sellier-Leclerc AL et al JASN 2007, 18:2392-400
Noris M et al Clin JASN 2010, 5:1844-59
Muus P et al EHA 2013

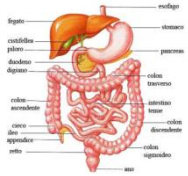
Manifestazioni extrarenali 20%

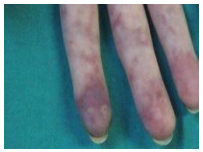
- Coinvolgimento Cardiovascolare
- Coinvolgimento SNC
- Coinvolgimento Polmonare
- Necrosi Digitali Distali
- Manifestazioni Gastrointestinali
- Disfunzione Surreni
- Emorragia oculare

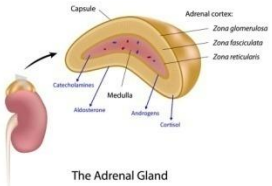




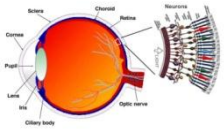






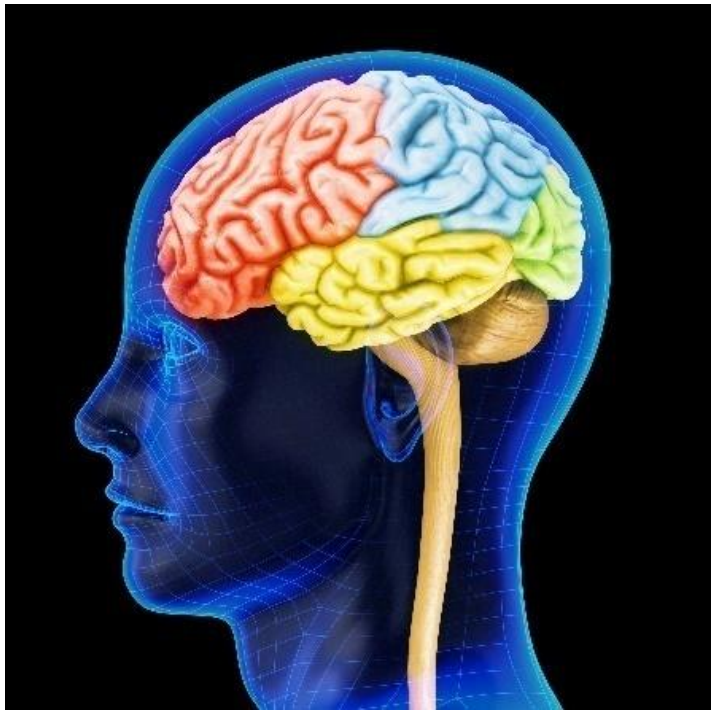


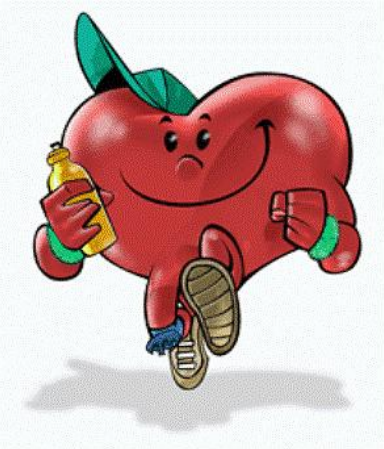
The Adrenal Gland



Coinvolgimento SNC (10%)

- Irritabilità
- Sonnolenza
- Convulsioni
- Diplopia
- Emiparesi o emiplegia
- Stato confusionale fino al coma





Cardiovascular complication

- Cardiac events (10%)
  - More rarely than TTP — Genetic or acquired CFH defects
  - Myocardial infarction
  - Cardiomyopathy — Transient disturbances of rhythm
  - Heart failure
- Vascular complication
  - Small peripheral artery thrombosis — Gangrenous lesions of distal phalanges of fingers and toes
  - Large artery stenosis — Cerebral arteries

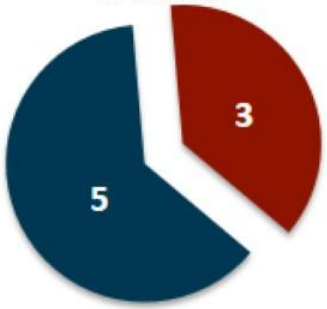
Vergouwen M et al AJNR 29, e34 (2008)
Noris M and Remuzzi G Nat. Rev. Nephrol. 10, 174-180(2014)

Thinking Outside the Kidney: In aHUS, Cardiovascular Complications Lead to Severe Morbidity and Premature Mortality

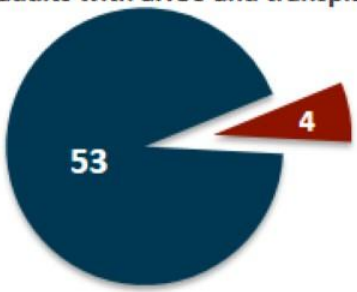
No indicated cardiovascular complications | Cardiovascular morbidity | Cardiovascular mortality

Cardiovascular events and myocardial infarction

n=8 aHUS[c]



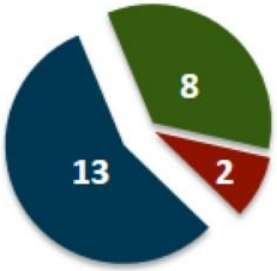
n=57 adults with aHUS and transplant[b]



- **A single patient** with aHUS died of myocardial infarction 15 days after aHUS onset[d]

Cardiomyopathy

n=23 pediatric patients with aHUS[f]



n=14[g]

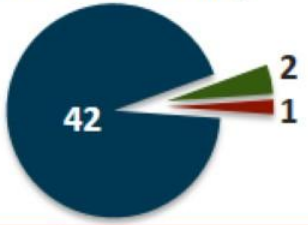
- **A single pediatric patient** had dilated cardiomyopathy at aHUS onset and myocardial dysfunction during follow-up monitoring[h]

Myocarditis

n=7 pediatric patients[e]

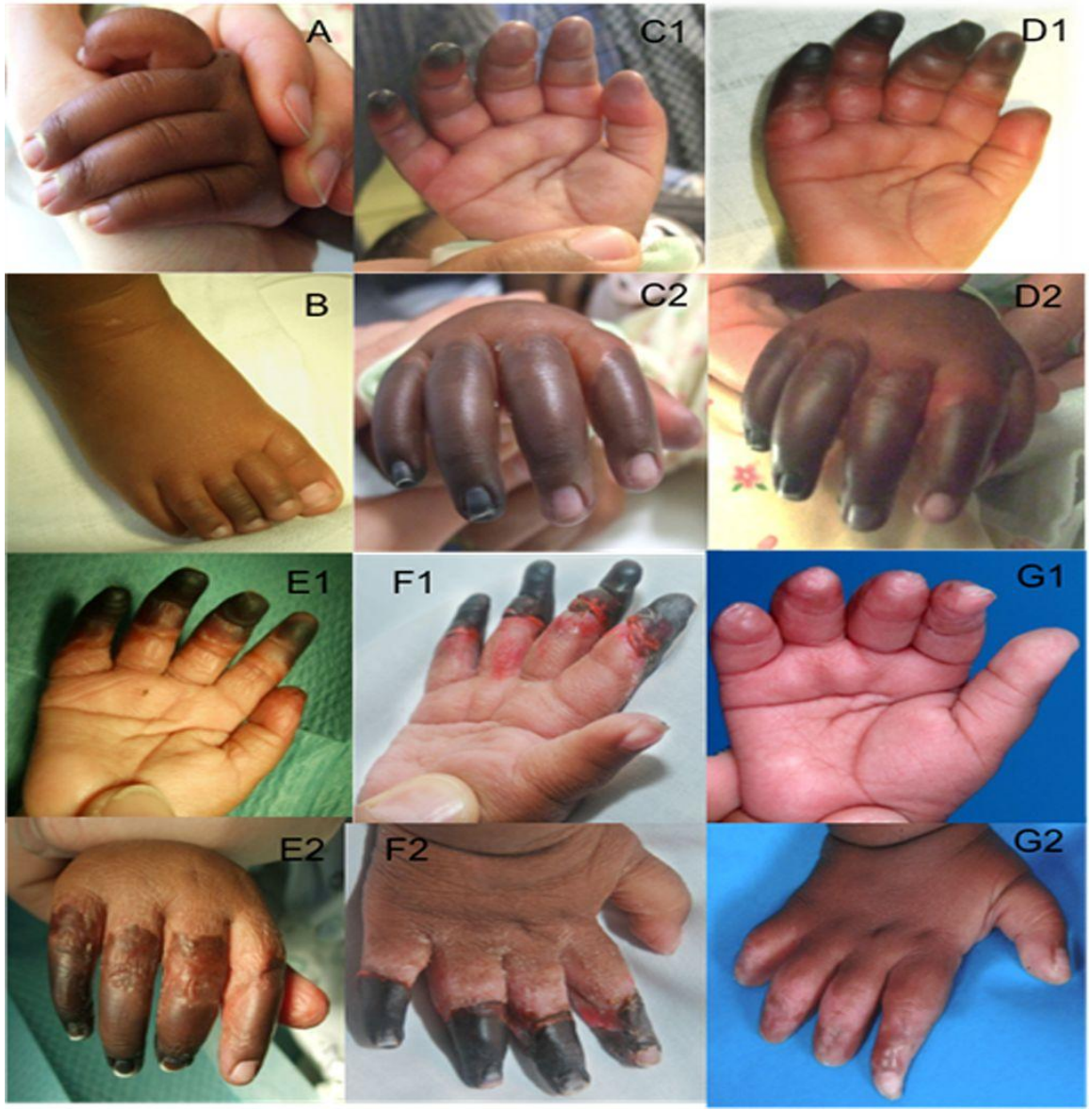
Cardiac insufficiency

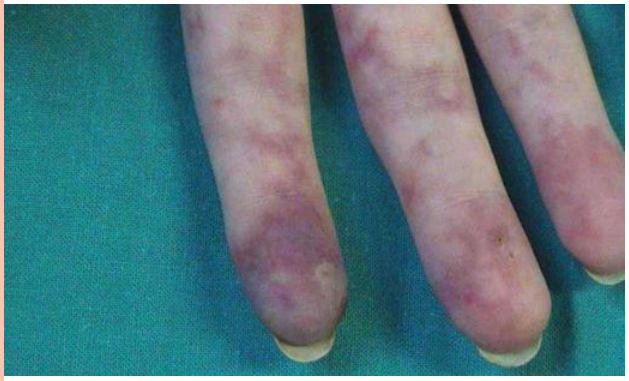
n=45[i]



a. Noris M. *Nat Rev Nephrol*. 2014;10:174-180; b. Le Quintrec M. *Am J Transplant*. 2013;13:663-675; c. Venables JP. *PLoS Med*. 2006;3:e431; d. Sallée M. *Nephrol Dial Transplant*. 2010;25:2028-2032; e. Abarrategui-Garrido C. *Blood*. 2009;114:4261-4271; f. Neuhaus TJ. *Arch Dis Child*. 1997;76:518-521; g. Roumenina LT. *Blood*. 2012;119:4182-4191; h. Vilalta R. *Pediatr Nephrol*. 2012;27:2323-2326; i. Dragon-Durey M-A. *J Am Soc Nephrol*. 2010;21:2180-2187; j. Loirat C. *Nephrol Dial Transplant*. 2010;25:3421-3425; k. Ažukaitis K. *Pediatr Nephrol*. 2014;29:1273-1277.

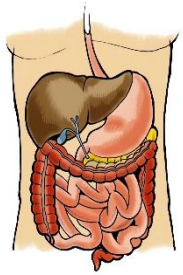
LESIONI GANGRENOSE DELLE ESTREMITA'





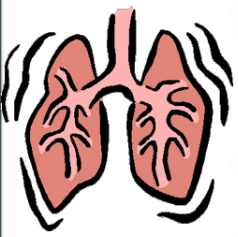
aHUS: Gastrointestinal Tract and Pulmonary Manifestations

Gastrointestinal



- Diarrhea, which may be bloody, an initial sign of STEC-HUS, is also an important trigger for aHUS.
- Abdominal colic, distention, constipation, strictures, pancolitis, and microperforations may be presenting signs.
- Pancreatic ischemia with pancreatitis or diabetes can occur.
- Elevated LFT results are present in 38% to 57% of cases at presentation.

Pulmonary



- Noted in some 30% of cases at first presentation; severe in up to 5% of cases, usually with multiorgan system involvement
- Pulmonary hemorrhage, edema, and pulmonary arterial hypertension
- Dyspnea, hemoptysis, and other signs may be confused with pneumonia or edema linked to acute kidney injury

Hofer J, et al. *Front Pediatr*. 2014;2:1-16.

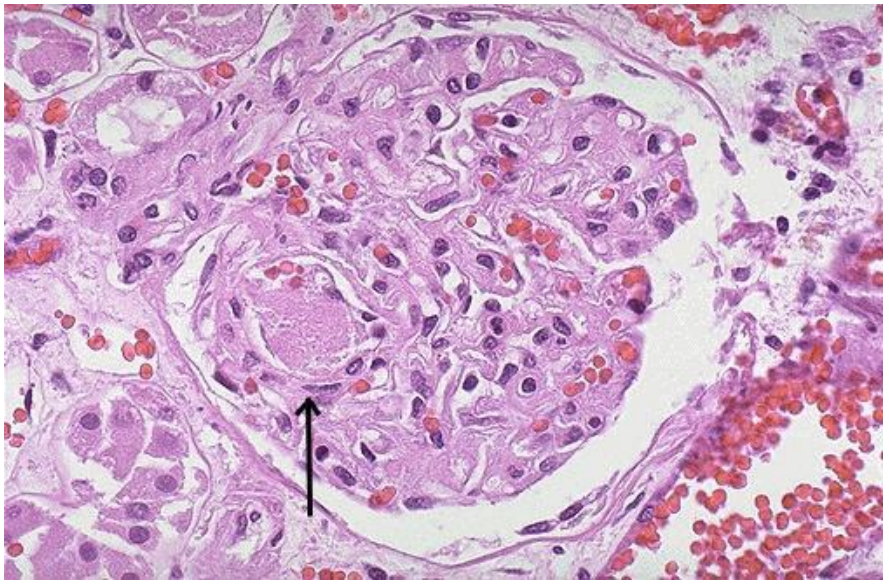
Alcuni pazienti non presentano né piastrinopenia né anemia

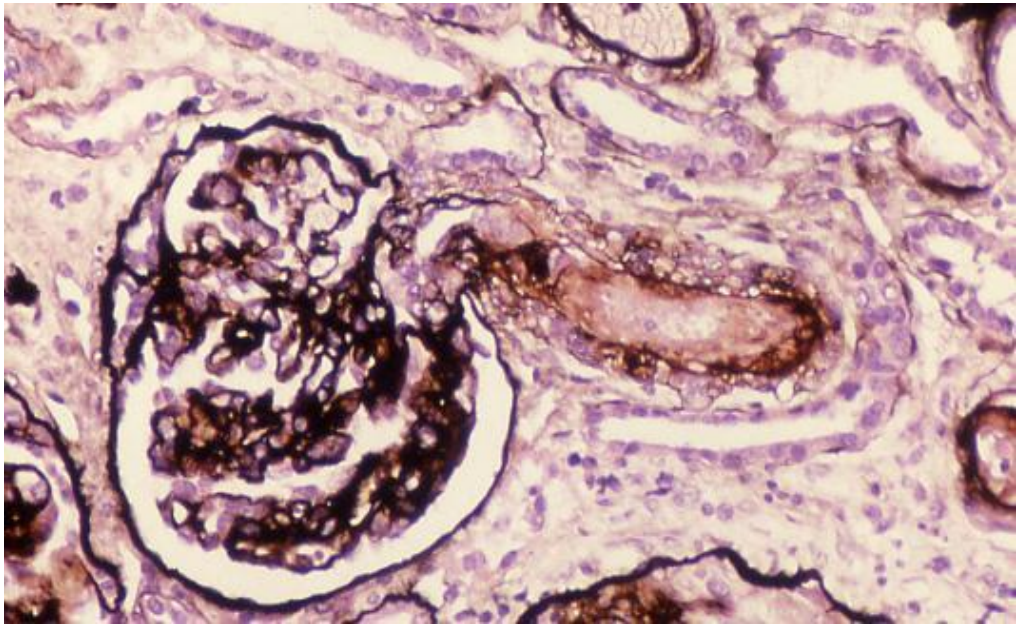
Le uniche manifestazioni di TMA sono:

- Ipertensione arteriosa
- Proteinuria
- Insufficienza renale progressiva

Biopsia renale

Ispessimento della parete di capillari ed arteriole





Trombi endoluminali

Mesangiolisi o necrosi del glomerulo con infiltrato infiammatorio

Prognosi

- 29% ESRD ad un anno di follow-up
- 56% decessi ad un anno di follow-up

Fremeaux Bacchi V et all. Clin J Am Soc Nephrol 2013; 8: 554-62

- 79% CKD, dialisi o morte nei 3 anni successivi alla diagnosi

Noris M et all. Clin J Am Soc Nephrol 2010;5:1844–59

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

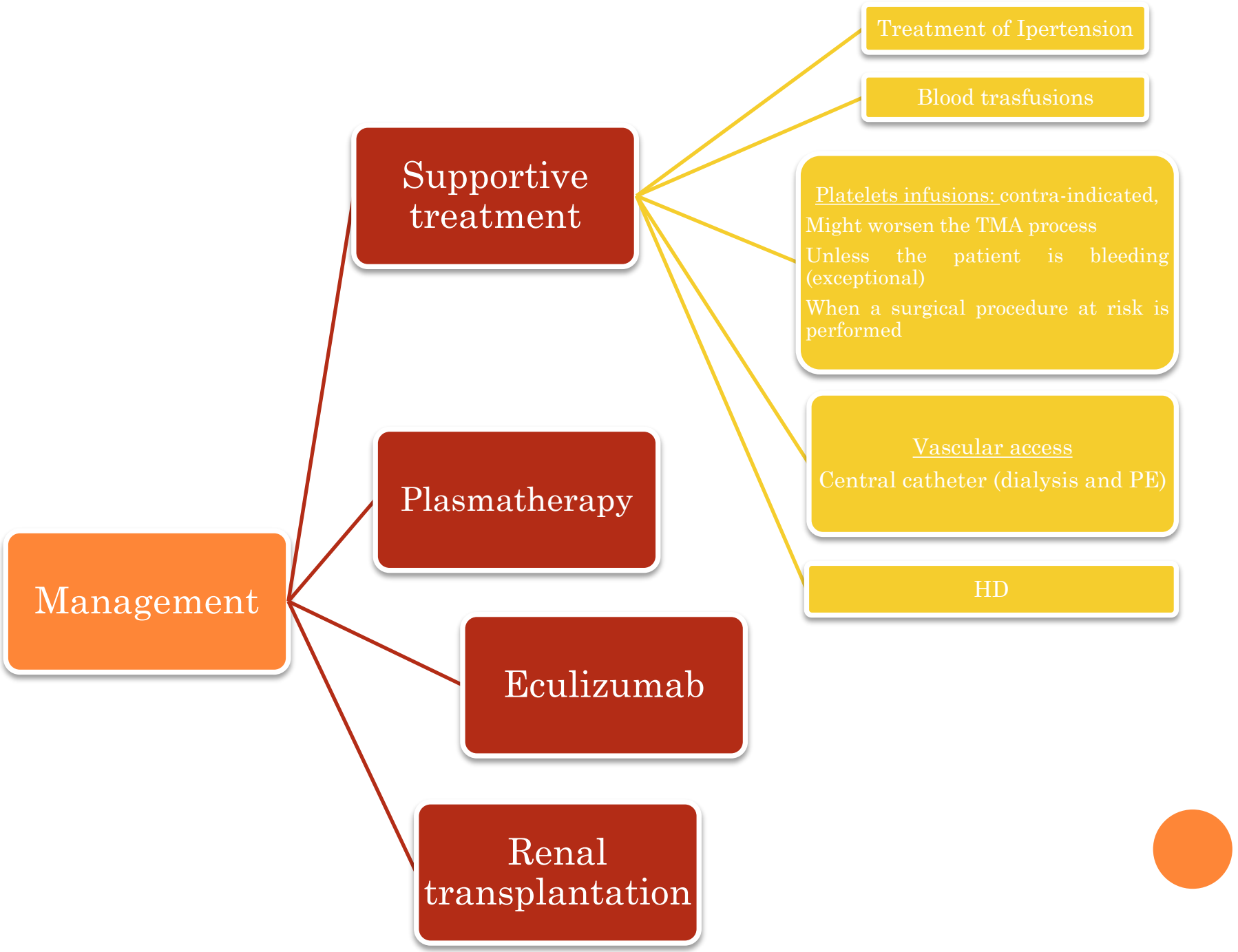
Atypical hemolytic uremic syndrome

Chantal Loirat[1*] and Véronique Frémeaux-Bacchi[2]

Table 3 Main clinical characteristics of patients with atypical hemolytic uremic syndrome according to complement abnormality

Gene or subgroup	Frequency in aHUS	Minimal age at onset		Risk of death or ESRD at 1st episode or within < 1 y	Risk of relapses	Risk of recurrence after renal transplantation	Plasma therapy indicated
		Children	Adults				
CFH	20-30%	Birth	any age	50-70%	50%	75-90%	Yes
CFI	4 -10%	Birth	any age	50%	10-30%	45-80%	Yes
MCP	5 -15%	> 1 y	any age	0-6%	70-90%	< 20%	Questionable
C3	2 -10%	7 m	any age	60%	50%	40-70%	Yes
CFB	1-4%	1 m	any age	50%	3/3 not in ESRD	100%	Yes
THBD	3 -5%	6 m	rare	50%	30%	1 patient	Yes
Anti-CFH Ab	6%	Mostly 7-11 y		30-40%	40-60%	Yes if high Ab titer	Yes (+ IS)

CFH: factor H; CFI: factor I; MCP: membrane cofactor protein; CFB: factor B; THBD: thrombomodulin; Ab, antibodies; ESRD: end stage renal disease; IS: immunosuppressive treatment.


Management
Supportive treatment
Treatment of Ipertension
Blood trasfusions
Platelets infusions: contra-indicated,
Might worsen the TMA process
Unless the patient is bleeding (exceptional)
When a surgical procedure at risk is performed
Vascular access
Central catheter (dialysis and PE)
HD
Plasmatherapy
Eculizumab
Renal transplantation

Plasma Exchange

- Terapia di prima linea dal 2010 che deve essere iniziata entro 24 ore dall'esordio
- Rimozione delle forme patologiche di CFH, CFI, CFB e C3, Ab anti-CFH e altri fattori responsabili della disfunzione endoteliale e dell'iperaggregabilità piastrinica
- Sostituzione con Plasma Fresco Congelato (apporto di CFH, CFI, CFB e C3)

CFH mutation	·63% had a response either complete or partial ·5% Recovery ·37% evolution to death or ESRD
CFI mutation	·25% had a response ·75% progressed to death or ESRF.
MCP/CD46	·Is not a circulating protein ·Questionable
C3, CFB or THBD mutation	·The benefit of plasmatherapy is scarcely documented ·C3 mutated: 57% Response Complete / partial ; 43% Death / ESRD ·THBD-mutated: 88% Response Complete / partial ; 12 % Death / ESRD
anti-CFH antibodies	·Titre often rises after PE ·Relapses of HUS frequently occur. ·immunosuppressive treatment is recommended, (steroids and azathioprine, mycophenolate mofetil, intravenous cyclophosphamide or anti-CD20)

Plasmatherapy

Noris M et al. Clin J Am Soc Nephrol 2010, 5:1844-1859.
Clark W. Semin Dial 2012;25:214-19

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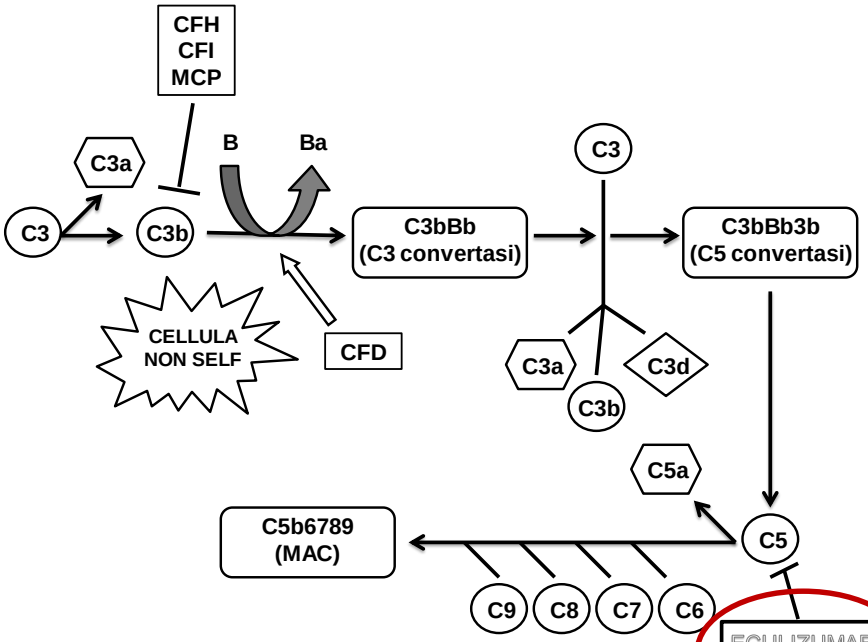
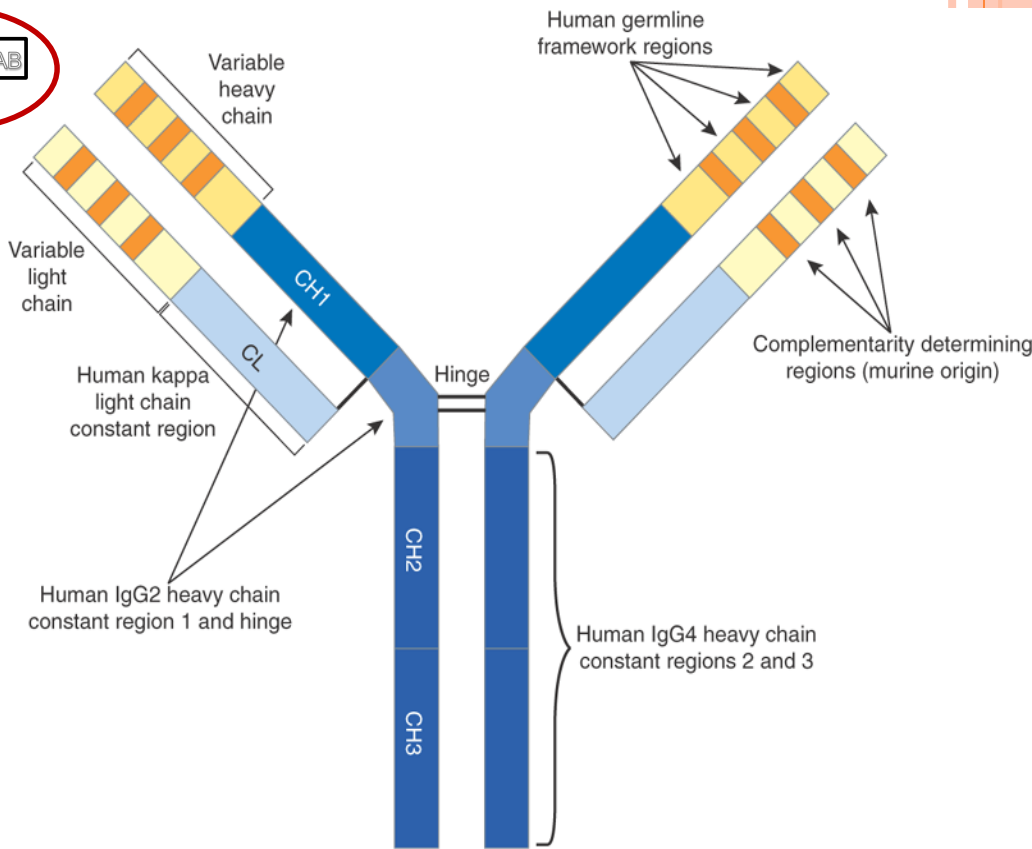
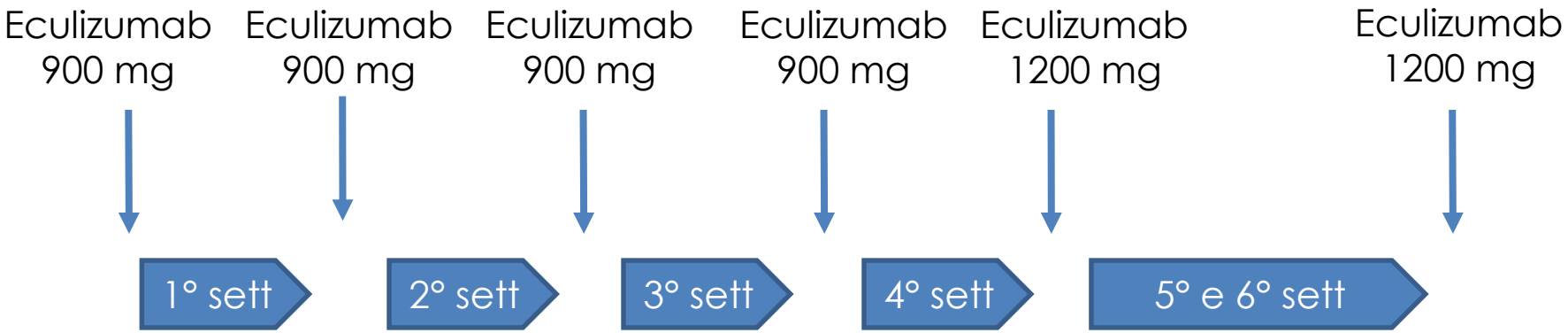

CFH
CFI
MCP
C3a
B
Ba
C3
C3b
C3bBb
(C3 convertasi)
C3
C3bBb3b
(C5 convertasi)
CELLULA
NON SELF
CFD
C3a
C3d
C3b
C5a
C5b6789
(MAC)
C5
C9
C8
C7
C6
ECULIZUMAB


Variable
heavy
chain
Human germline
framework regions
Variable
light
chain
CH1
CL
Hinge
Complementarity determining
regions (murine origin)
Human kappa
light chain
constant region
CH2
CH3
Human IgG2 heavy chain
constant region 1 and hinge
Human IgG4 heavy chain
constant regions 2 and 3

ECULIZUMAB

Emivita 11-12 giorni ⇨ somministrazione bisettimanale



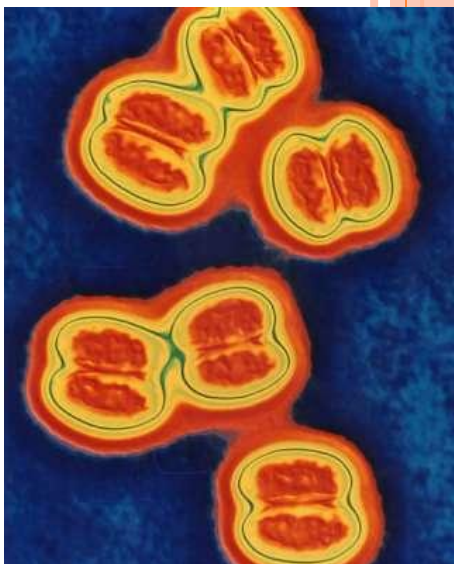
aHUS

- 50 µg/mL

Infezione da Nisseriae Meningitidis

- Il blocco della via terminale del complemento induce un aumentato rischio di infezione da Nisseriae Meningitidis
- I pazienti devono ricevere una vaccinazione per Nisseriae Meningitidis prima di iniziare terapia con Eculizumab
- Profilassi antibiotica per due settimane

MENVEO ⇨ Vaccinazione contro ceppi A, C, W, Y
BEXSERO ⇨ Vaccinazione contro ceppo B



Effetti Collaterali di Eculizumab

- Cefalea
- Mal di schiena
- Nausea
- Ipertensione arteriosa
- Infezione delle alte vie respiratorie
- Diarrea
- Vomito
- Infezione delle vie urinarie
- Leucopenia
- Anemia

ECULIZUMAB & SEUA

2009-2013

Complement Inhibitor Eculizumab in Atypical Hemolytic Uremic Syndrome

Christoph J. Mache,* Birgit Acham-Roschitz,* Veronique Frémeaux-Bacchi,† Michael Kirschfink,‡ Peter F. Zipfel,§ Siegfried Roedl,* Udo Vester,‖ and Ekkehard Ring*
*Department of Pediatrics, Medical University Graz, Graz, Austria; †Service d'Immunologie Biologique, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, and Cordeliers Research Center, INSERM UMRS 872, Paris, France; and ‡Institute of Immunology, University of Heidelberg, Heidelberg, §Department of Infection, Hans Knoell Institute for Natural Products Research and Friedrich Schiller University of Jena, Jena, and ‖Clinic of Pediatric Nephrology, University of Duisburg-Essen, Essen, Germany

Eculizumab in atypical hemolytic uremic syndrome: long-term clinical course and histological findings

Sibylle Tschumi · Mathias Gugger · Barbara S. Bucher · Magdalena Riedl · Giacomo D. Simonetti

Long-term eculizumab improves clinical outcomes in atypical hemolytic uremic syndrome

Ramon Vilalta · Enrique Lara · Alvaro Madrid · Sara Chocron · Marina Muñoz · Alex Casquero · Jose Nieto

Efficacy of eculizumab in a patient with factor-H-associated atypical hemolytic uremic syndrome

Anne-Laure Lapeyraque · Véronique Frémeaux-Bacchi · Pierre Robitaille

Eculizumab in atypical haemolytic–uraemic syndrome allows cessation of plasma exchange and dialysis

Jon Jin Kim, Simon C. Waller and Christopher J. Reid

Preservation of Renal Function in Atypical Hemolytic Uremic Syndrome by Eculizumab: A Case Report

AUTHORS: Mario Giordano, MD,[a] Giuseppe Castellano, MD, PhD,[b] Giovanni Messina, MD,[a] Claretta Divella, PhD,[b] Rosa Bellantuono, MD,[a] Flora Puteo, MD,[a] Vincenzo Colella, MD,[a] Tommaso Depalo, MD,[a] and Loreto Gesualdo, MD[b]
[a]Pediatric Nephrology and Dialysis Unit, Ospedale Pediatrico Giovanni XXIII, Bari, Italy; and [b]Nephrology, Dialysis and Transplantation Unit, Policlinico di Bari, University of Bari, Bari, Italy

Early treatment with eculizumab in atypical haemolytic uraemic syndrome

Maria Garjau[1], María Azancot[1], Rosa Ramos[1], Pilar Sánchez-Corral[2], Maria Angeles Montero[3] and Daniel Serón[1]

New Treatment Options for Atypical Hemolytic Uremic Syndrome with the Complement Inhibitor Eculizumab

Özlem Köse, M.D.,[1] Lothar-Bernd Zimmerhackl, M.D., Ph.D.,[2] Therese Jungraithmayr, M.D.,[2] Christoph Mache, M.D.,[3] and Jens Nürnberger, M.D.[1]

Eculizumab as rescue therapy for atypical hemolytic uremic syndrome with normal platelet count

Eiske M. Dorresteijn · Nicole C. A. J. van de Kar · Karlien Cransberg

Eculizumab therapy in a child with hemolytic uremic syndrome and CFI mutation

F. Semsa Caycı · Nilgun Cakar · Veysel Sabri Hancer · Nermin Uncu · Banu Acar · Gokce Gur

Eculizumab therapy for atypical haemolytic uraemic syndrome due to a gain-of-function mutation of complement factor B

Rodney D. Gilbert · Darren J. Fowler · Elizabeth Angus · Stephen A. Hardy · Louise Stanley · Timothy H. Goodship

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

2 studi multicentrici, prospettici, open-label, di fase II

- Trial 1: 17 aHUS R a plasmaferesi o infusione di PFC
- Trial 2: 20 aHUS in tp cronica con plasmaferesi o infusione di PFC con plt stabili

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

2 studi multicentrici, prospettici, open-label, di fase II

- Normalizzazione plt (dopo 7 gg nel trial 1 e dopo 26 settimane del trial 2) e indici di emolisi
- Interruzione terapia con plasma
- Miglioramento fx renale
- Miglioramento Quality of life

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These two clinical studies suggest that long-term eculizumab treatment is effective in patients with atypical hemolytic–uremic syndrome, with earlier intervention associated with a greater clinical benefit. The data indicate that terminal complement inhibition with eculizumab inhibits complement-mediated thrombotic microangiopathy, decreases the need for thrombotic microangiopathy–related intervention, significantly improves the platelet count and renal function across patient groups, and is associated with substantial kidney recovery and improved clinical outcomes in patients with atypical hemolytic–uremic syndrome.

N Engl J Med 2013;368:2169-81.

kidney INTERNATIONAL
Official journal of the International Society of Nephrology

Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies

Christoph Licht[1], Larry A. Greenbaum[2], Petra Muus[3], Sunil Babu[4], Camille L. Bedrosian[5], David J. Cohen[6], Yahsou Delmas[7], Kenneth Douglas[8], Richard R. Furman[9], Osama A. Gaber[10], Timothy Goodship[11], Maria Herthelius[12], Maryvonne Hourmant[13], Christophe M. Legendre[14], Giuseppe Remuzzi[15], Neil Sheerin[16], Antonella Trivelli[17] and Chantal Loirat[18]

In conclusion, 2-year analyses of these trials demonstrated that longer-term eculizumab therapy maintained inhibition of complement activity, TMA, and improvements in hematologic parameters and renal function. Furthermore, eculizumab continued to prevent progression to end-stage renal disease in the majority of patients with aHUS.

Kidney International (2015) 87, 1061–1073

Notevole miglioramento outcome ematologico e renale

Costi elevati

Non noti effetti a lungo termine

Necessità di individualizzare il trattamento

Discontinuation of Eculizumab

Official Journal of the National Kidney Foundation

AJKD American Journal of Kidney Diseases

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome: A Report of 10 Cases

Gianluigi Ardissino, MD, PhD, Sara Testa, MD, Ilaria Possenti, MD, Francesca Tel, MD, Fabio Paglialonga, MD, Stefania Salardi, BS, Silvana Tedeschi, MD, Mirco Belingheri, MD, and Massimo Cugno, MD

"…3 of the 10 pts experienced relapse within 6 weeks of discontinuation, but then immediately resumed treatment and completely recovered…"

"…5 patients experienced relapse…within 6 months of the last eculizumab dose…Eleven patients remained in remission with no signs of acute disease…"

Discontinuation of Eculizumab Treatment in Atypical Hemolytic Uremic Syndrome: An Update

Gianluigi Ardissino, MD, PhD, Ilaria Possenti, MD
Francesca Tel, MD, Sara Testa, MD, Stefania Salardi, BS
Vito Ladisa, PharmD

In conclusion, we believe that in atypical hemolytic uremic syndrome, it is possible and relatively safe to discontinue eculizumab therapy. In general, we discourage discontinuation of eculizumab therapy in kidney transplant recipients with *CFH* mutations and patients with glomerular filtration rates < 20 mL/min/1.73 m^2. In patients with anti-CFH antibodies, we consider discontinuation of eculizumab therapy when antibody titer is <2.5 times the upper limit of normal. We suggest regular home urine dipstick monitoring for early identification of relapses, especially during acute illnesses and when patients feel unwell.

Discontinuation of Eculizumab

National Kidney Foundation
AJKD American Journal of Kidney Diseases

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome

Jack F.M. Wetzels, MD, PhD, Nicole C.A.J. van de Kar, MD, PhD
Radbound University Medical Center, Nijmegen, the Netherlands

"…eculizumab treatment was withdrawn in 3 of our patients, 2 of whom had no signs of disease activity…Recurrent disease developed in 1 patients 3 months after eculizumab discontinuation…"

Can eculizumab be discontinued in aHUS?

Case report and review of the literature

Tuncay Sahutoglu, MD[a,*], Taner Basturk, MD[a], Tamer Sakaci, MD[a], Yener Koc, MD[a], Elbis Ahbap, MD[a], Mustafa Sevinc, MD[a], Ekrem Kara, MD[b], Cuneyt Akgol, MD[a], Feyza Bayraktar Caglayan, MD[a], Abdulkadir Unsal, MD[a], Moha…

patients with MCP mutations, homozygous CFHR3/R1 deletions, anti-CFH antibodies, no identifiable mutations and CFI mutations carry a low risk, whereas CFH mutations pose a major risk of recurrence of TMA following discontinuation of eculizumab in patients with aHUS. Preinjury markers of

Table 1
Summary of aHUS cases who were treated with and discontinued eculizumab.

Study	Patient number	Age at onset of aHUS, sex	Kidney (native or transplanted)	Complement abnormality	Duration of eculizumab treatment before discontinuation (months)	Method of follow-up	TM recurrence, time, mo	Retreatment with eculizumab	Outcome (creatinine, proteinuria)
Alachkar et al, 2012[24]	1	24, F	Transplant 2nd	None	1.9	Unreported	Yes, 5	Yes	Graft loss
Cayci et al, 2012[19]	2	10,F	Native	CFI	0.75	Unreported	No, 4	No	Good (0.5 mg/dL, unreported)
Gulleroglu et al, 2013[14]	3	6, F	Native	MCP	1.25	Unreported	No, 9	No	Good (normal renal functions, unreported)
Carr et al, 2013[25]	4	20, F	Native	CFH	9	Unreported	Yes, 6	Yes	Dialysis-free (values unreported)
Pu et al, 2014[21]	5	85, F	Native	None	3	Unreported	No, 12	No	Good (normal renal functions)
Wetzels et al, 2015[22]	6	30, F	Unreported	CFH	35	Unreported	No, 17	No	Stable
	7	21, F	Unreported	CFH	4.5	Unreported	Yes, 3	Yes	Unreported
	8	43, F		CFH	4	Unreported	No, 11	No	Stable
Ardissino et al, 2015[10]	9	4.3, M	Unreported	CFH	6.7	Home-based urine dipstick test thrice weekly to detect microscopic hematuria	Yes, 1.5	Yes	Good (0.57 mg/dL, not detectable)
	10	37.7, F	Unreported	CFH+CFI+THBD	14.4		Yes, 0.9	Yes	Good (1.16mg/dL, 1.12 mg/mg)
	11	52.7, M	Unreported	CFI	1.5		No, 40	No	Good (0.78 mg/dL, 0.22 mg/mg)
	12	34.8, F	Unreported	CFI	10.4		No, 28.2	No	Good (2.11 mg/dL, 1.30 mg/mg)
	13	2.6, M	Unreported	CFI	5.6		Yes, 17.3	Yes	Good (0.45mg/dL, 0.31 mg/mg)
	14	1.3, F	Unreported	CFHR3/R1 del/del	13.4		No, 23.7	No	Good (0.24mg/dL, 3.81 mg/mg)
	15	19.1, M	Unreported	Anti-CFH+	5.5		No, 31.4	No	Good (1.13mg/dL, 0.15 mg/mg)
	16	5.4, F	Unreported	MCP	0.5		No, 31.2	No	Good (0.54mg/dL, 0.20 mg/mg)
	17	13.3, M	Unreported	Anti-CFH+CFHR3/R1 del/del	2.6		No, 25.8	No	Good (0.8 mg/dL, 0.19mg/mg)
	18	10.9, F	Unreported	CFH+CFHR3/R1 del/del +Anti-CFH	0.9		Yes, 1.2	Yes	Good (0.8 mg/dL, 0.07 mg/mg)
	19	44, F	Unreported	None	4.1		No, 24.7	No	Good (0.84 mg/dL, not detectable)
	20	52, F	Unreported	CFHR3/R1 del/del	8.3		No, 8.9	No	Good (2.3 mg/dL, not detectable)
	21	60, M	Unreported	None	4.5		No, 7.2	No	Good (1.1 mg/dL, not detectable)
	22	15.8, F	Unreported	Anti-CFH+CFHR3/R1 del/del	0.8		Yes, 0.7	Yes	Good (0.83 mg/dL, 0.74 mg/mg)
	23	1.7, M	Unreported	MCP	0.5		No, 0.7	No	Good (0.68 mg/dL, 0.16 mg/mg)
	24	40.8, F	Unreported	None	0.6		No, 0.4	No	Good (0.81 mg/dL, 0.33 mg/mg)

aHUS = atypical hemolytic uremic syndrome, CFI = complement factor I, CFH = complement factor H, CFHR = complement factor H-related protein, MCP = membrane cofactor protein, THBD = thrombomodulin, TMA = thrombotic microangiopathy.

Therapeutic drug monitoring of Eculizumab

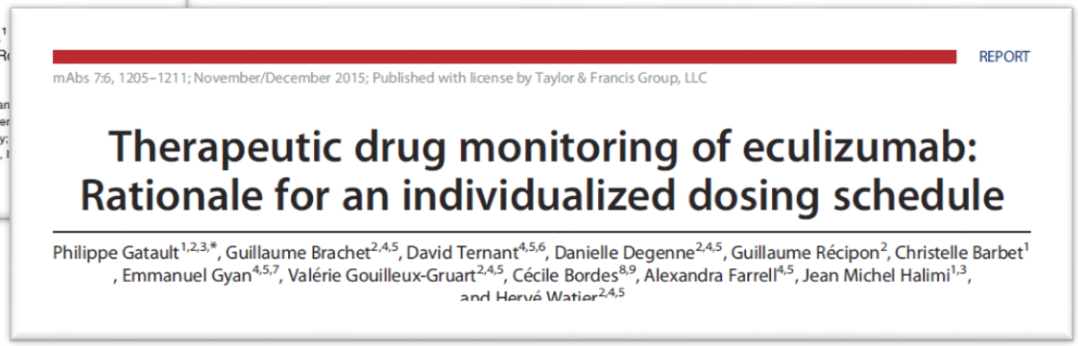
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Dynamics of complement activation in aHUS and how to monitor eculizumab therapy

Marina Noris,[1] Miriam Galbusera,[1] Sara Gastoldi,[1] Paolo Macor,[2] Federica Banterla,[1] Elena Bresin,[1] Serena Bettoni,[1] Roberta Donadelli,[1] Elisabetta Valoti,[1] Francesco Tedesco,[4] Alessandro Amore,[5] R Piero Ruggenenti,[6] Eliana Gotti,[6] and Giuseppe Remuzzi[1,6]

[1]IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri," Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," Ran "Centro Anna Maria Astori" Science and Technology Park Kilometro Rosso, Bergamo, Italy; [2]Department of Life Sciences, Univer Italy; [3]Tumor Immunology Unit, Human Pathology Section, Department of Health Sciences, University of Palermo, Palermo, Italy; Auxologico Italiano, Milan, Italy; [5]Unit of Nephrology, Dialysis and Transplantation, Regina Margherita University Hospital, Turin, I Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy

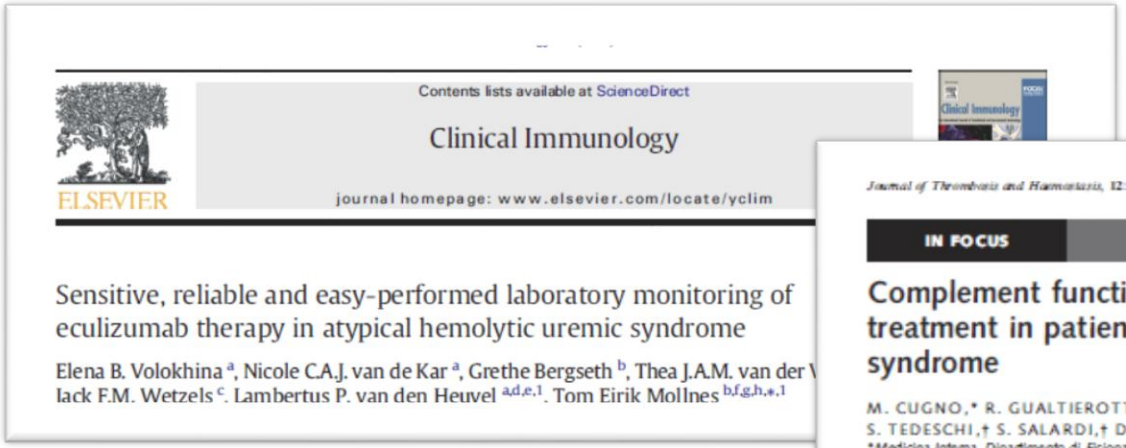


REPORT

mAbs 7:6, 1205–1211; November/December 2015; Published with license by Taylor & Francis Group, LLC

Therapeutic drug monitoring of eculizumab: Rationale for an individualized dosing schedule

Philippe Gatault[1,2,3,*], Guillaume Brachet[2,4,5], David Ternant[4,5,6], Danielle Degenne[2,4,5], Guillaume Récipon[2], Christelle Barbet[1], Emmanuel Gyan[4,5,7], Valérie Gouilleux-Gruart[2,4,5], Cécile Bordes[8,9], Alexandra Farrell[4,5], Jean Michel Halimi[1,3], and Hervé Watier[2,4,5]



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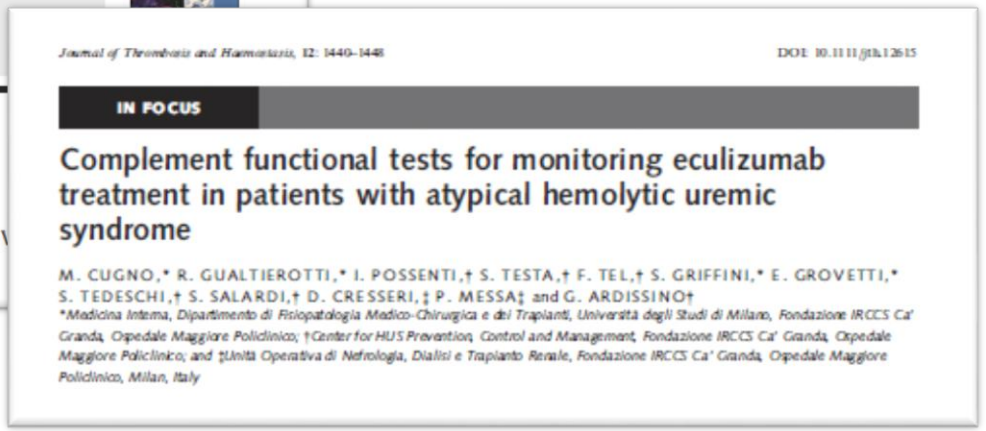
Sensitive, reliable and easy-performed laboratory monitoring of eculizumab therapy in atypical hemolytic uremic syndrome

Elena B. Volokhina [a], Nicole C.A.J. van de Kar [a], Grethe Bergseth [b], Thea J.A.M. van der V Jack F.M. Wetzels [c], Lambertus P. van den Heuvel [a,d,e,1], Tom Eirik Mollnes [b,f,g,h,*,1]



Journal of Thrombosis and Haemostasis, 12: 1440–1448 DOI: 10.1111/jth.12615

IN FOCUS

Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome

M. CUGNO,* R. GUALTIEROTTI,* I. POSSENTI,† S. TESTA,† F. TEL,† S. GRIFFINI,* E. GROVETTI,* S. TEDESCHI,† S. SALARDI,† D. CRESSERI,‡ P. MESSA‡ and G. ARDISSINO†

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Nine adult patients who received eculizumab for aHUS or PNH

→ Measurement of eculizumab trough levels

→ Pharmacokinetic study

The following weight-based schedule could be proposed

90 to 120 kg:	• 1200 mg every 2 weeks;
70 to 90 kg:	• 1200 mg every 4 weeks;
<70 kg:	• 1200 mg every 6 weeks.

Trapianto di rene

- Rischio di ricorrenza di aHUS intorno al 50%
- Correlato con il tipo di anomalia genetica
- 80-90% Rischio di perdita del graft in caso di recidiva

Mutazione	% Rischio di recidiva
CFH	75-90
CFI	45-80
C3	40-70
CFB	100 ma soli 3 pz
THBD	nv
MCP	15-20
Ab anti-CFH	Correlato al titolo Ab

Lorait C and Frémeaux-Bacchi V OJRD 2011,6:60

Trapianto di rene da vivente consanguineo non raccomandato!

- **Controindicato** sia nei pz con mutazione nota sia non nota

- Considerare il rischio che il donatore sviluppi a HUS dopo la donazione del rene

Recidiva post-trapianto

- Eculizumab + efficace di PEX nel trattamento delle recidive post-trapianto
- “Plasmaferesi preventiva”

- Eculizumab un’ora prima del tpx in pazienti ad elevato rischio di recidiva

Nel futuro…

- Inibitori di C5 → molecole di piccole dimensioni con minore attività immunogena e potenziale assorbimento intestinale
- Concentrato plasma-derivato umano
- CFH ricombinante
- Ab anti-properdina

SISET

SOCIETA' ITALIANA PER LO STUDIO DELL'EMOSTASI E DELLA TROMBOSI

XXIV CONGRESSO NAZIONALE SISET

9/12 NOVEMBRE 2016

TEATRO PIETRO D'ABANO
ABANO TERME (PD)

Grazie per l'attenzione!