MICROANGIOPATIE TROMBOTICHE:
PATOGENESI/TERAPIA
PERUGIA, 29 SETTEMBRE 2016

La sindrome emolitico-uremica atipica ed il ruolo del nefrologo

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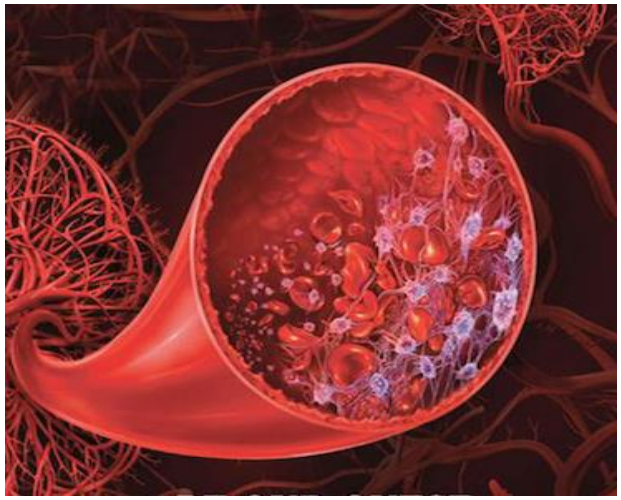
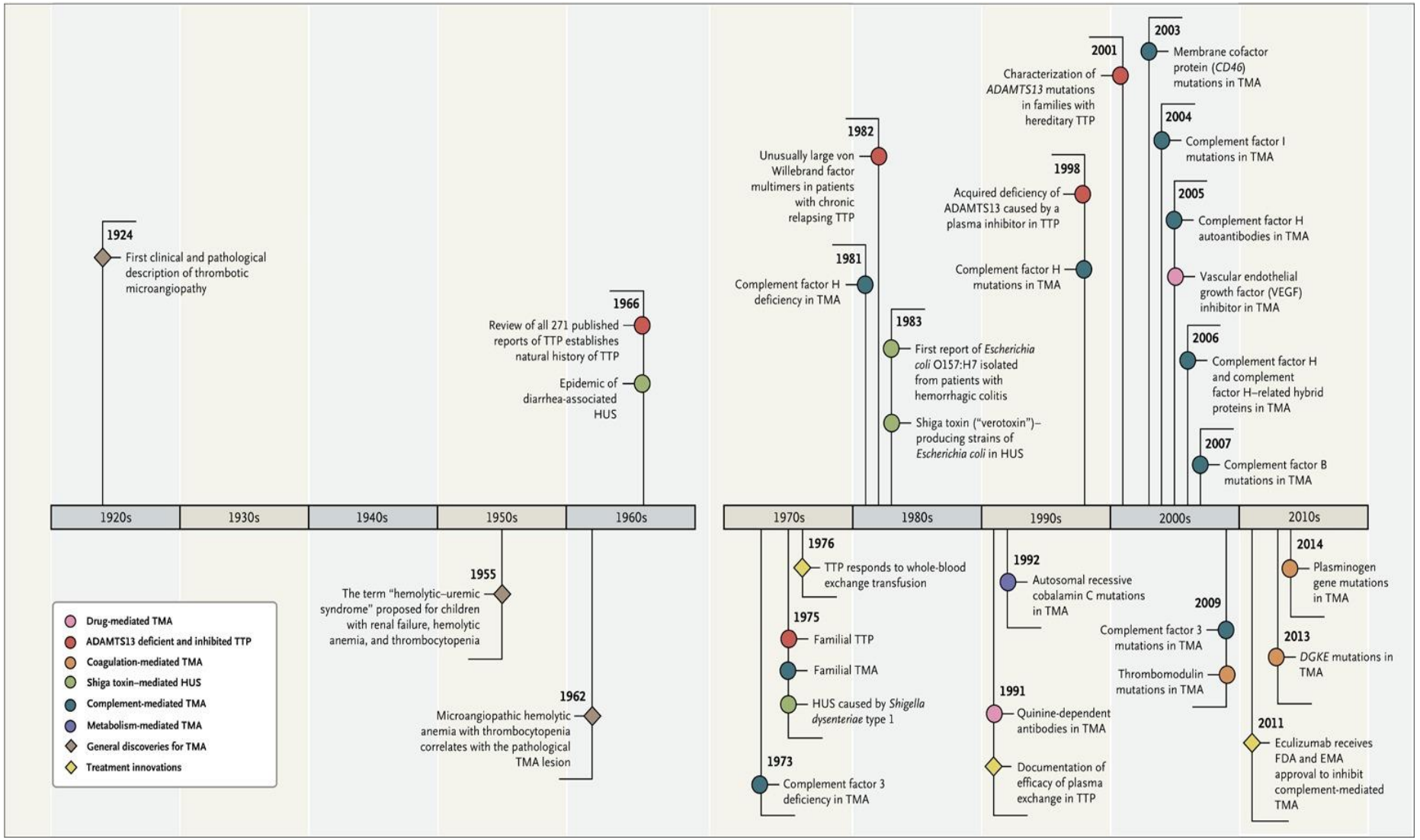
Definizione di Sindrome emolitico-uremica atipica (aSEU)



Cronistoria delle Microangiopatie Trombotiche TMA



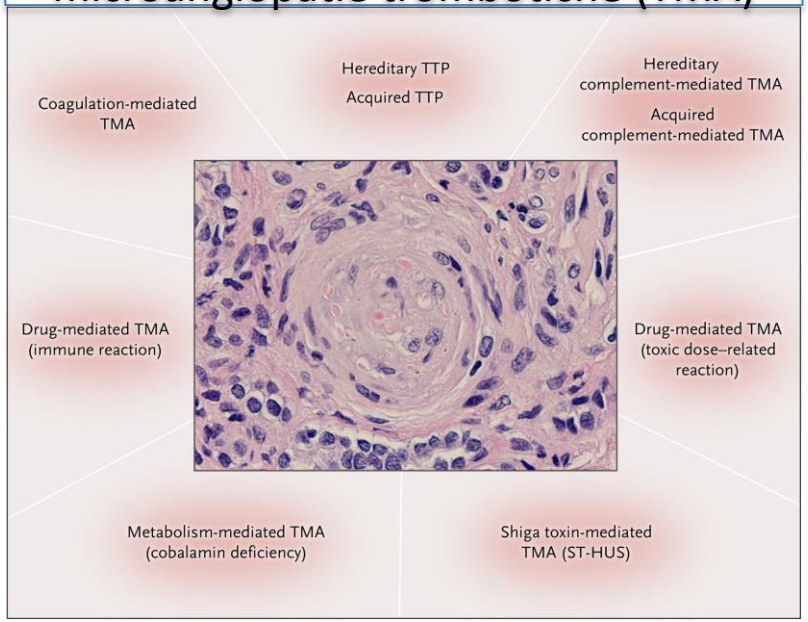
George JN, Nester CM. N Engl J Med 2014;371:654-666

The NEW ENGLAND JOURNAL of MEDICINE

Definizione di Sindrome emolitico-uremica SEU/HUS

- Anemia emolitica non-immunologica (T di Coombs negativo)
- Trombocitopenia (Plt < 150.000/mmc)
- Insufficienza renale acuta (adulto: AKI sec. KDIGO,RIFLE e AKIN bambino:^creatinina 1.5 volte i valori di riferimento per età e sesso)

Quadro istopatologico comune nelle microangiopatie trombotiche (TMA)



George JN, Nester CM. N Engl J Med 2014;371:654

Definizione di Sindrome emolitico-uremica atipica aSEU/HUS

Table 1 | Classification of HUS, TTP, and related disorders

Part 1: etiology advanced	
1.i	*Infection induced* (a) Shiga and verocytotoxin (shiga-like toxin)-producing bacteria; enterohemorrhagic *Escherichia coli*, Shigella dysenteriaen type 1, *Citrobacter* (b) *Streptococcus pneumoniae*, neuraminidase, and T-antigen exposure
1.ii	*Disorders of complement regulation,* (a) Genetic disorders of complement regulation (b) Acquired disorders of complement regulation, for example anti-FH antibody
1.iii	*von Willebrand proteinase, ADAMTS13 deficiency* (a) Genetic disorders of ADAMTS13 (b) Acquired von Willebrand proteinase deficiency; autoimmune, drug induced
1.iv	*Defective cobalamine metabolism*
1.v	*Qinine induced*
Part 2: Clinical associations: etiology unknown	
2.i	HIV
2.ii	Malignancy, cancer chemotherapy and ionizing radiation
2.iii	Calcineurin inhibitors and transplantation
2.iv	Pregnancy, HELLP syndrome and oral contraceptive pill
2.v	Systemic lupus erythematosis and antiphospholipid antibody syndrome
2 vi	Glomerulopathy
2.vii	Familial, not included in part 1
2.viii	Unclassified

FH, factor H; HELLP, HEmolytic anemia, elevated Liver enzymes, and Low Platelets; HIV, human immunodeficiency virus; HUS, hemolytic uremic syndrome; TTP, thrombocytopenic purpura.

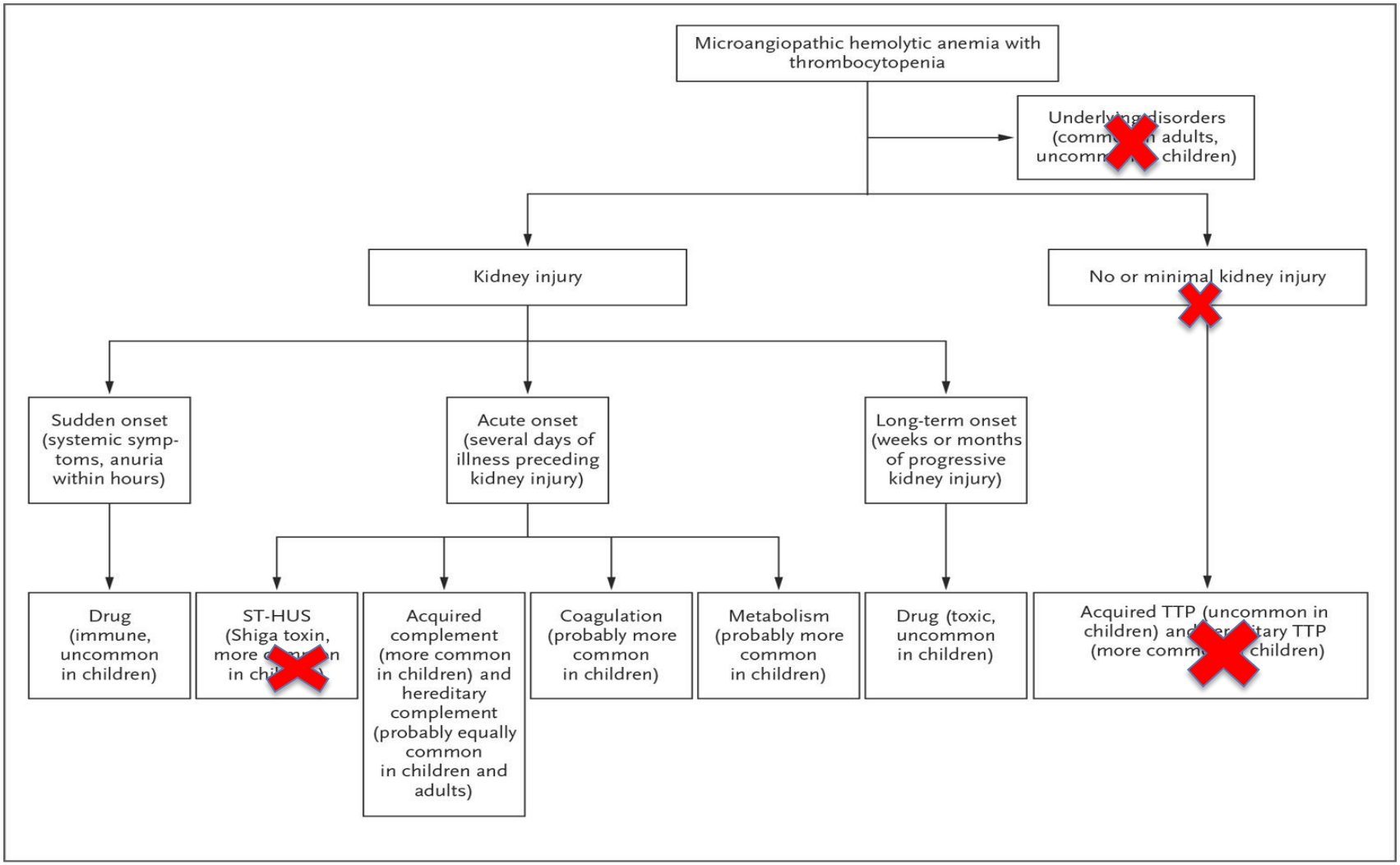
N Besbas et al.: Classification of HUS and TTP and related disorders Kidney International(2006) 70, 423–431.

Table 1. Classification of Atypical Hemolytic–Uremic Syndrome.*

Form of Disease	Complement Abnormalities
Familial	Mutations in *CFH*, 40–45%; in *CFI*, 5–10%; in *C3*, 8–10%; in *MCP*, 7–15%; in *THBD*, 9%; and in *CFB*, 1–2%.
Sporadic	
Idiopathic	Mutations in *CFH*, 15–20%; in *CFI*, 3–6%; in *C3*, 4–6%; in *MCP*, 6–10%; in *THBD*, 2%; and in *CFB*, 2 cases; anti-CFH antibodies: 6–10%
Pregnancy-associated	Mutations in *CFH*, 20%; in *CFI*, 15%
HELLP syndrome	Mutations in *CFH*, 10%; in *CFI*, 20%; and in *MCP*, 10%
Drugs	Rare *CFH* mutations (mostly unknown)
Organ transplantation	Mutations in *CFH*, 15%; in *CFI*, 16%
Human immunodeficiency virus infection	Unknown†
Cancer	Unknown†

M. Noris and G. Remuzzi. N Engl J Med 2009;361:1676-87.

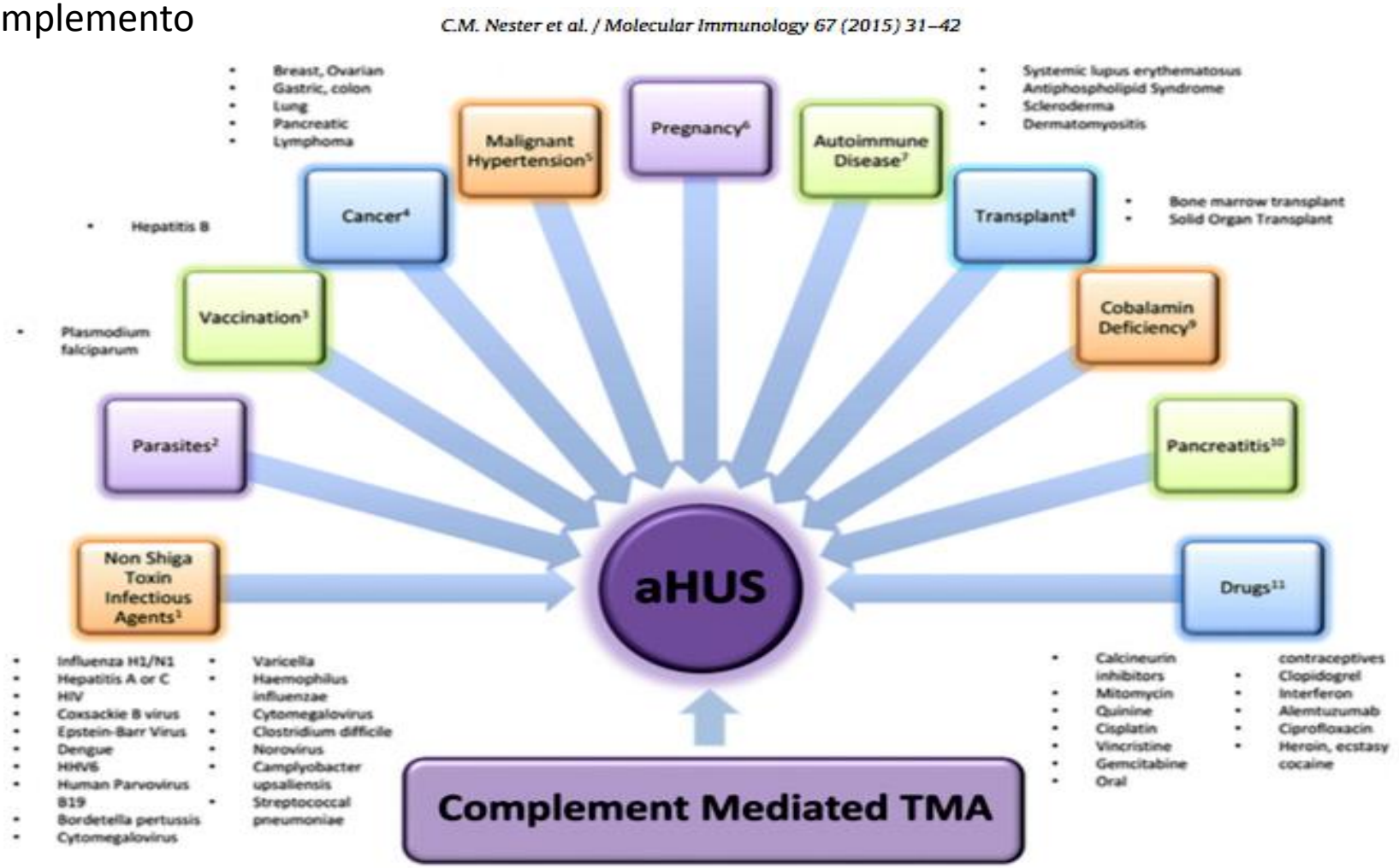
Definizione di Sindrome emolitico-uremica atipica aSEU/HUS



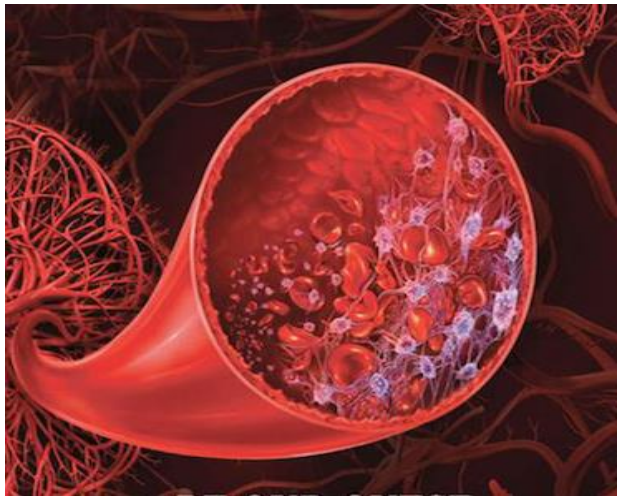
George JN, Nester CM. N Engl J Med 2014;371:654-666

Definizione di Sindrome emolitico-uremica atipica aSEU/HUS

-Gruppo eterogeneo di malattie microangiopatiche accomunate dalla disregolazione del complemento



Epidemiologia della Sindrome emolitico-uremica atipica (aSEU)

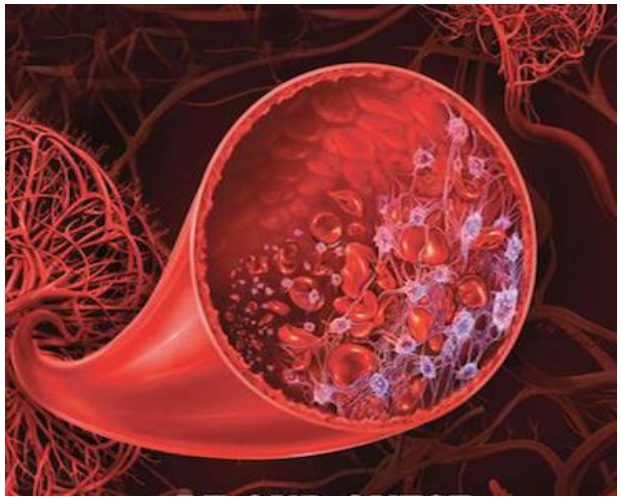


Epidemiologia della Sindrome emolitico-uremica atipica (aSEU)

-Incidenza 1-2/1.000.000
-5-10% dei casi di SEU
-età pediatrica M=F
-età adulta F>M
-ogni età è interessata

- Sellier-Leclerc AL. J Am Soc Nephrol 2007, 18:2392-2400
- Noris M. Clin J Am Soc Nephrol 2010,5:1844-1859
- Sullivan M. Ann Hum Genet 2010, 74:17-26
- Westra D. Nephrol Dial Transplant 2010, 25:2195-2202
- Maga TK, Human Mutat 2010,31:E 1445-1460
- Fremeaux-Bacchi V. Clin J Am Soc Nephrol 2013,8:554-562

Quadri clinici della Sindrome emolitico-uremica atipica (aSEU)



Quadri clinici della Sindrome emolitico-uremica atipica (aSEU)

- Esordio subdolo
- Astenia, malessere, inappetenza, vomito
- Ipertensione arteriosa, insufficienza cardiaca, IMA [20%]
- Oliguria, ematuria, edema, insufficienza renale
- Irritabilità, convulsioni, diplopia, emiparesi, stupor, coma [10%]
- Diarrea /gastroenterite [80% pz pediatrici, 23-50% pz adulti]
- Eventi scatenanti: infezioni tratto respiratorio, gravidanza [20%]

Al Laboratorio

- ❑ Anemia : Hb <10g/dl - schistociti - ^^LDH - < aptoglobina
- ❑ Piastrinopenia < 150.000/mmc
- ❑ ++ creatinina rispetto ai VN per età

Noris M et al Clin J Am Soc Nephrol 2010. 5: 1844–1859
Loirat C Orphanet J of Rare Disease 2011,6:60-

Quadri clinici della Sindrome emolitico-uremica atipica (aSEU)

Table 2. Patient characteristics

Patients	Genetic Abnormalities					CFH Ab ($n = 8$)	None ($n = 134$)
	CFH ($n = 65$)	CFI ($n = 10$)	C3 ($n = 12$)	THBD ($n = 13$)	MCP ($n = 18$)		
Disease onset	**(65)**	**(10)**	**(12)**	**(13)**	**(18)**	**(8)**	**(130)**
Children (≤18 years)	39	4	6	12	14	6	71
Adults (>18 years)	26	6	6	1	4	2	59
Male/female	30/24	4/6	7/5	7/3	12/6	4/4	61/72
Familial/sporadic	35/30[a]	4/6	4/8	7/6[a]	5/13	0/8	21/113
Recurrences	28 (55)[a]	1 (10)[b]	6 (12)	3 (10)	13 (18)[a]	3/8	36 (129)
Triggering/underlying conditions	**(41)**	**(8)**	**(11)**	**(5)**	**(15)**	**(7)**	**(104)**
Diarrhea/gastroentheritis	6	2	2	1	5	1	28
Upper respiratory tract infections	9	2	1	2	3	4	14
Malignancy and cancer chemotherapy	—	—	—	—	—	—	1
Malignant hypertension	4	—	—	—	—	—	12
De novo post-transplant HUS	1	1	—	—	—	—	8
Pregnancy related HUS	3	2	—	—	—	—	8
Systemic disease	1	—	—	—	—	—	2
Glomerulopathy	2	1	1	—	—	—	4
Extrarenal manifestations	**14 (49)**	**3 (9)**	**1 (11)**	**1 (10)**	**0 (18)**	**1 (7)**	**22 (107)**
Multivisceral involvement[c]	4	1	0	1	0	0	6
Cardiovascular disease only	5	0	0	0	0	0	2
Central nervous system only	5	2	1	0	0	1	14
Biochemical evaluation							
Reduced C3 serum levels (≤83 mg/dl)	23 (49)[a]	2 (10)	8 (11)[a]	4 (8)	4 (15)	3 (7)	22 (103)
Reduced C4 serum levels C4 (≤15 mg/dl)	2 (48)	0 (10)	2 (10)	1 (7)	1 (15)	1 (7)	6 (103)
Reduced CFH serum levels (≤350 mg/L)	6 (46)	0 (10)	0 (9)	0 (6)	0 (15)	2 (7)	2 (104)

Noris M et al Clin J Am Soc Nephrol 2010. 5: 1844–1859

• Quadri clinici della Sindrome emolitico-uremica atipica (aSEU)

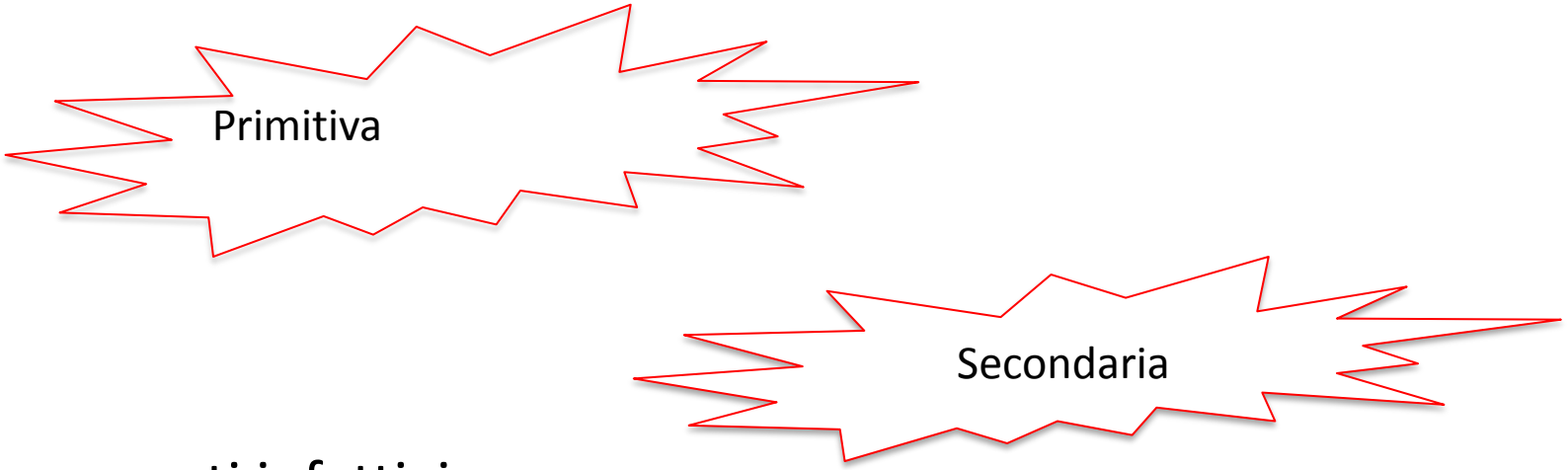
Table 1 | Clinical characteristics at onset in children with Shiga toxin-producing *E. coli*-associated, anti-CFH autoantibody-associated, or atypical HUS

Clinical characteristics at onset	STEC-HUS[12]	Anti-CFH autoantibody-associated HUS[4,11,a]	aHUS with or without complement abnormalities[2,b]
Age	Mostly 6 months to 5 years	Mostly 5–13 years	MCP mutation: >1 year, mostly 2–12 years CFH and CFI mutation: mostly <2 years C3 mutation and no complement abnormality identified: any age DGKE mutation:[c] all <1 year
Diarrhea	95% Severe colitis: 10%	9.4%[11] to 53%[4] Abdominal pain and vomiting: 84%[4]	39%
Progressive onset	No	No	Possible
Complete triad[d]	~95%	100%	74%
Acute renal failure	95%, dialysis required in 50%	100%, dialysis required in 57%[4] to 86%[11]	85%, dialysis required in 60%
Neurological symptoms[e]	20%	23%[4] to 40.6%[11]	16%
Pancreatitis (elevated amylasemia/lipasemia)	10%	23%[4]	7%
Hepatitis (elevated transaminases ± jaundice)	10%	50%[4] to 57.3%[11]	6%
Cardiac involvement[f]	2-5%	Possible	2%
Familial HUS history	Simultaneous occurrence or a few days or weeks apart (familial contamination)	No	27% Complement mutations: autosomal dominant inheritance DGKE mutations: autosomal recessive inheritance

Sinha A, Kidney Int 2014; 85: 1151–1160.

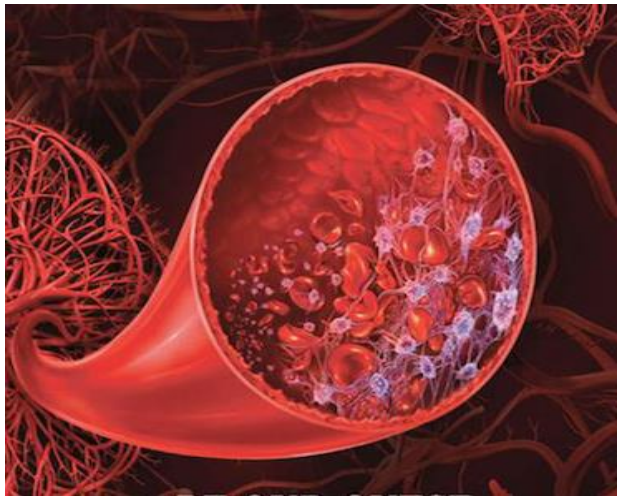
C Loirat and V.Fre´meaux-Bacchi Kidney International (2014) 85, 1019–1022

Quadri clinici della Sindrome emolitico-uremica atipica (aSEU)

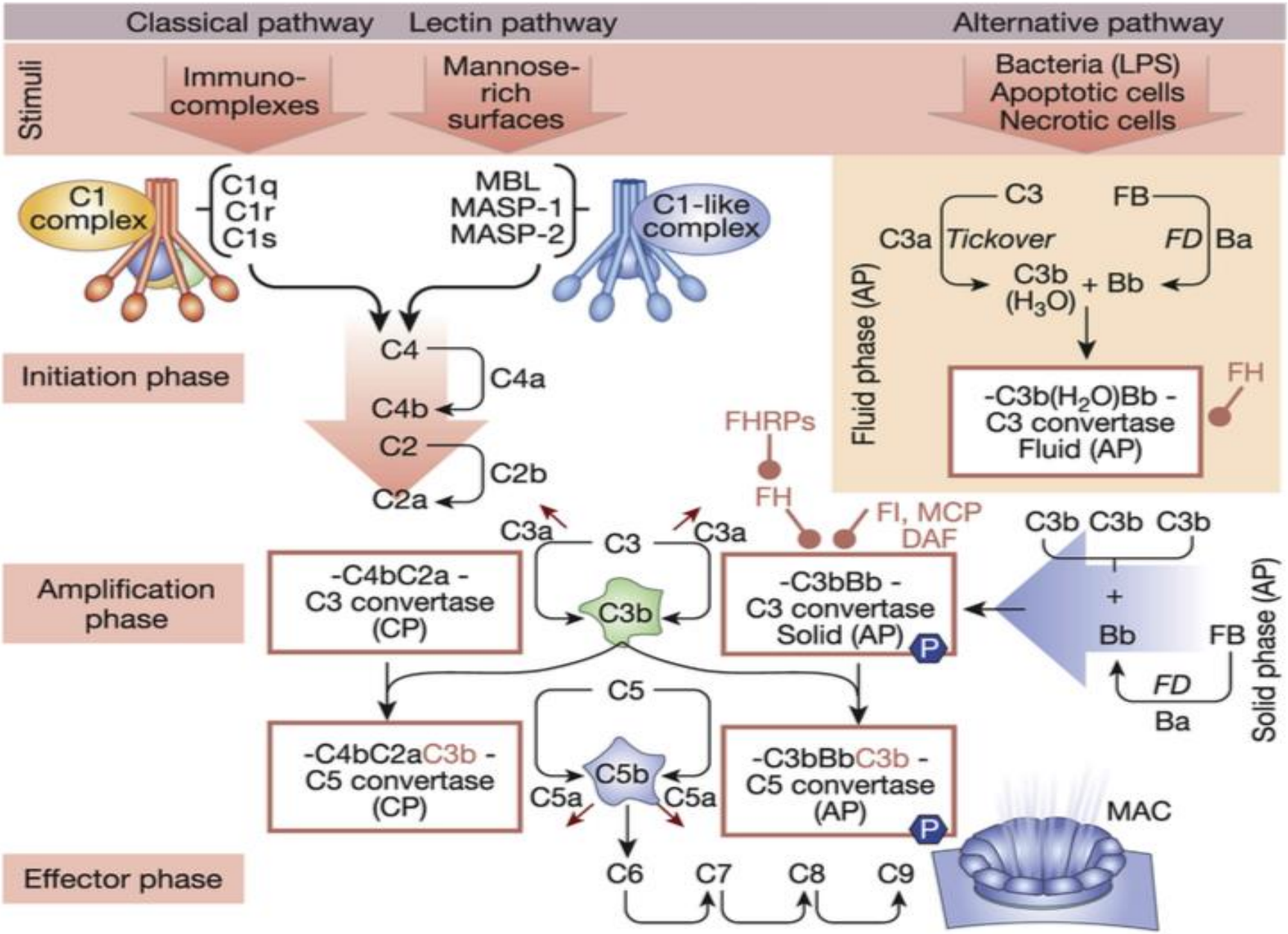


- agenti infettivi
- Farmaci: chinino , inibitori della calcineurina, cisplatino, vincristina, gemcitabina (ruolo del complemento non chiarito)
- Gravidanza
- M. autoimmuni : LES, APS
- Cancro 16.9% (ruolo del complemento non chiarito)
- Trapianto : midollo osseo, organi solidi
- Anomalie metaboliche: carenza di cobalamina C

Patogenesi della Sindrome emolitico-uremica atipica (aSEU)

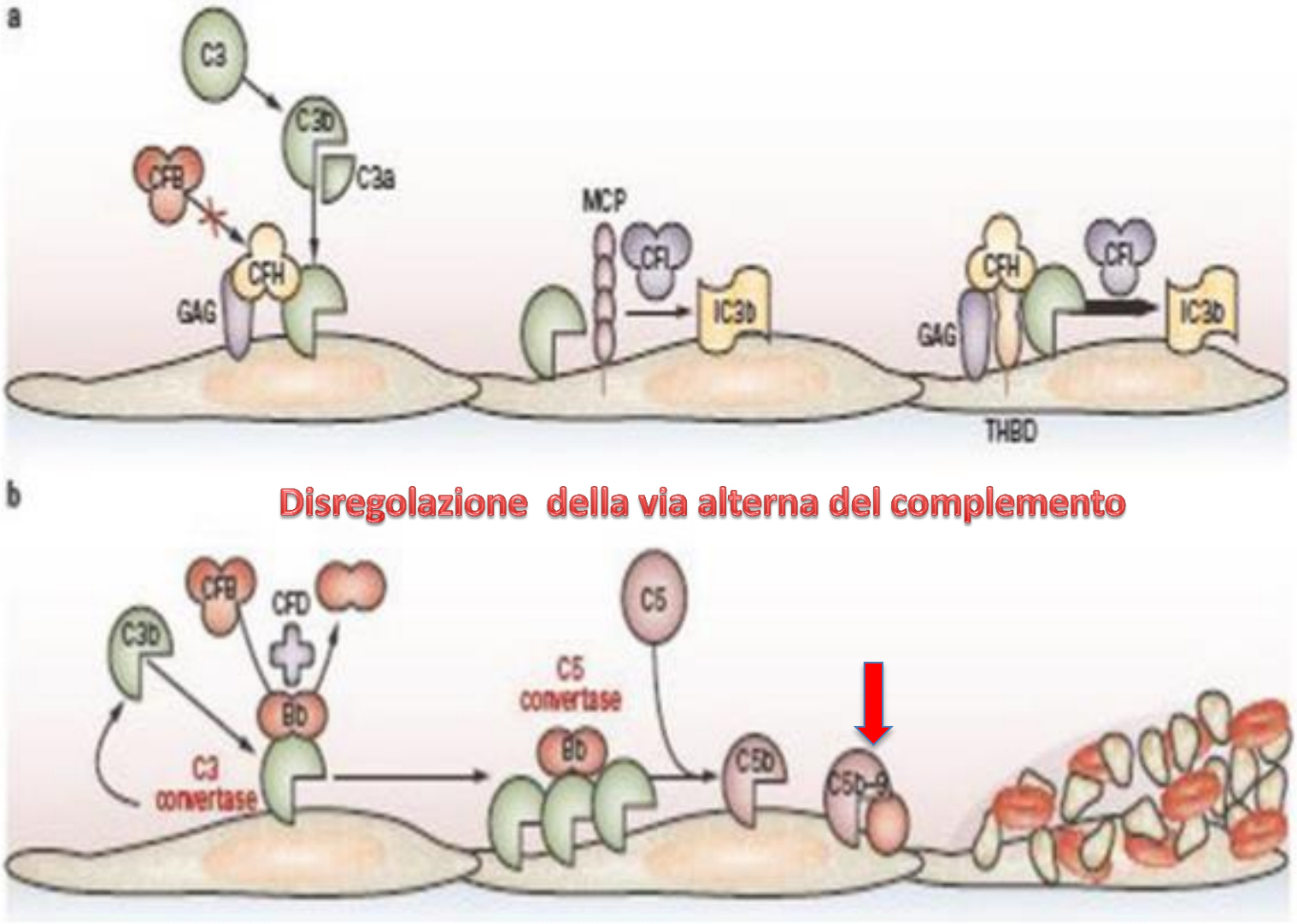


Schema della normale via del complemento



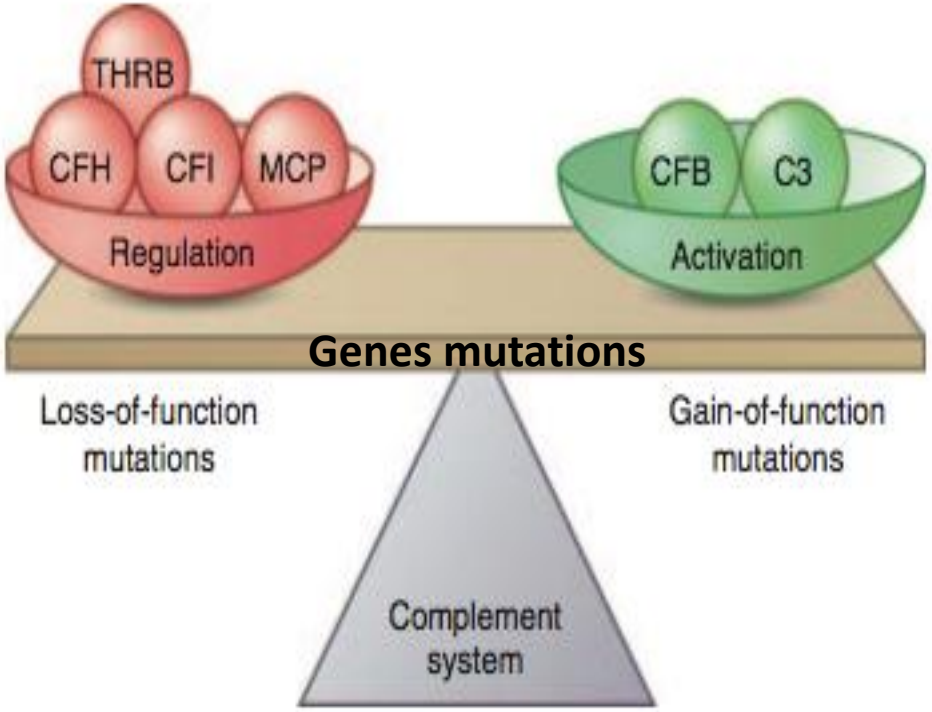
Angioi A. Kidney International (2016) 89, 278–288

Normale attivazione della via alterna del complemento



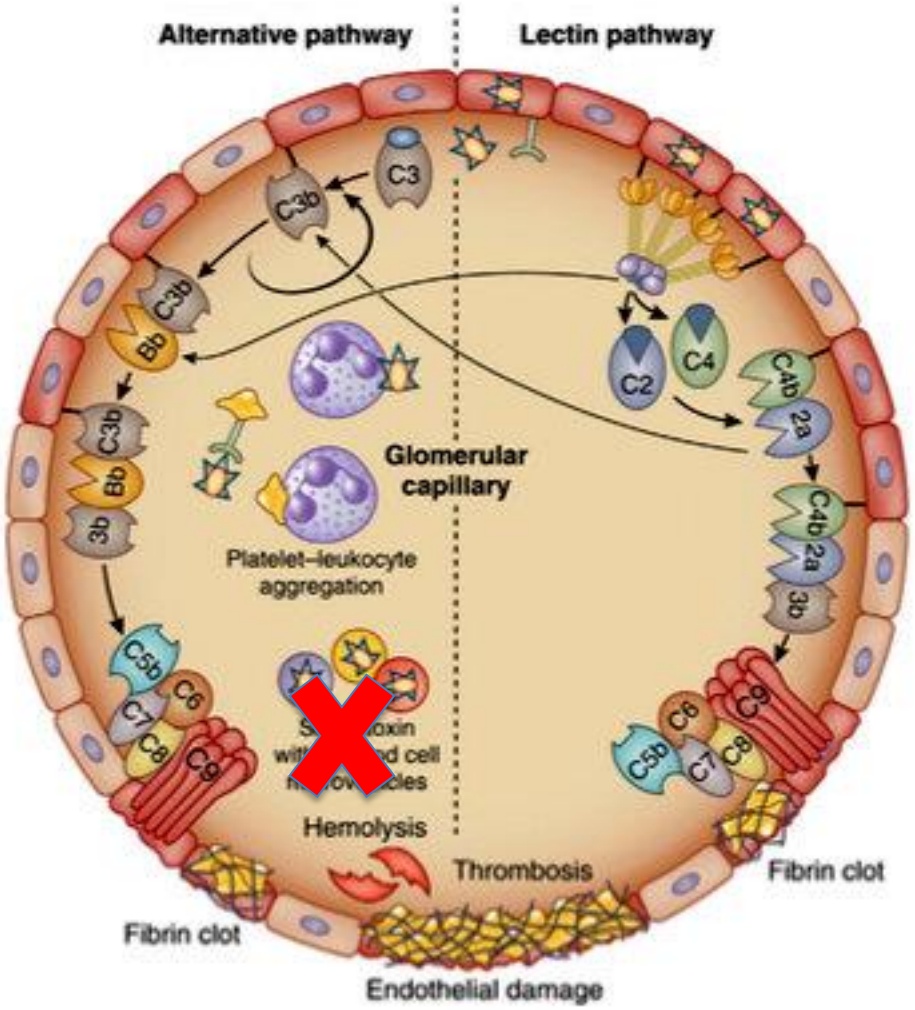
Loirat and Frémeaux-Bacchi Orphanet Journal of Rare Diseases 2011, 6:60

Mutazioni del complemento nella aSEU



E. Goicoechea de Jorge. Kidney International (2010) **78,** 721–723

Attivazione del complemento in un capillare glomerulare , nella SEU tipica indotta da Shiga-toxin



aSEU

- Suscettibilità genetica
- Fattori scatenanti (infezioni, farmaci, gravidanza)
- Amplificazione della via alterna del complemento

Table 1. Kidney Diseases Associated With Mutations or Variations in Genes for Complement Regulatory Proteins, Categorized by Syndrome

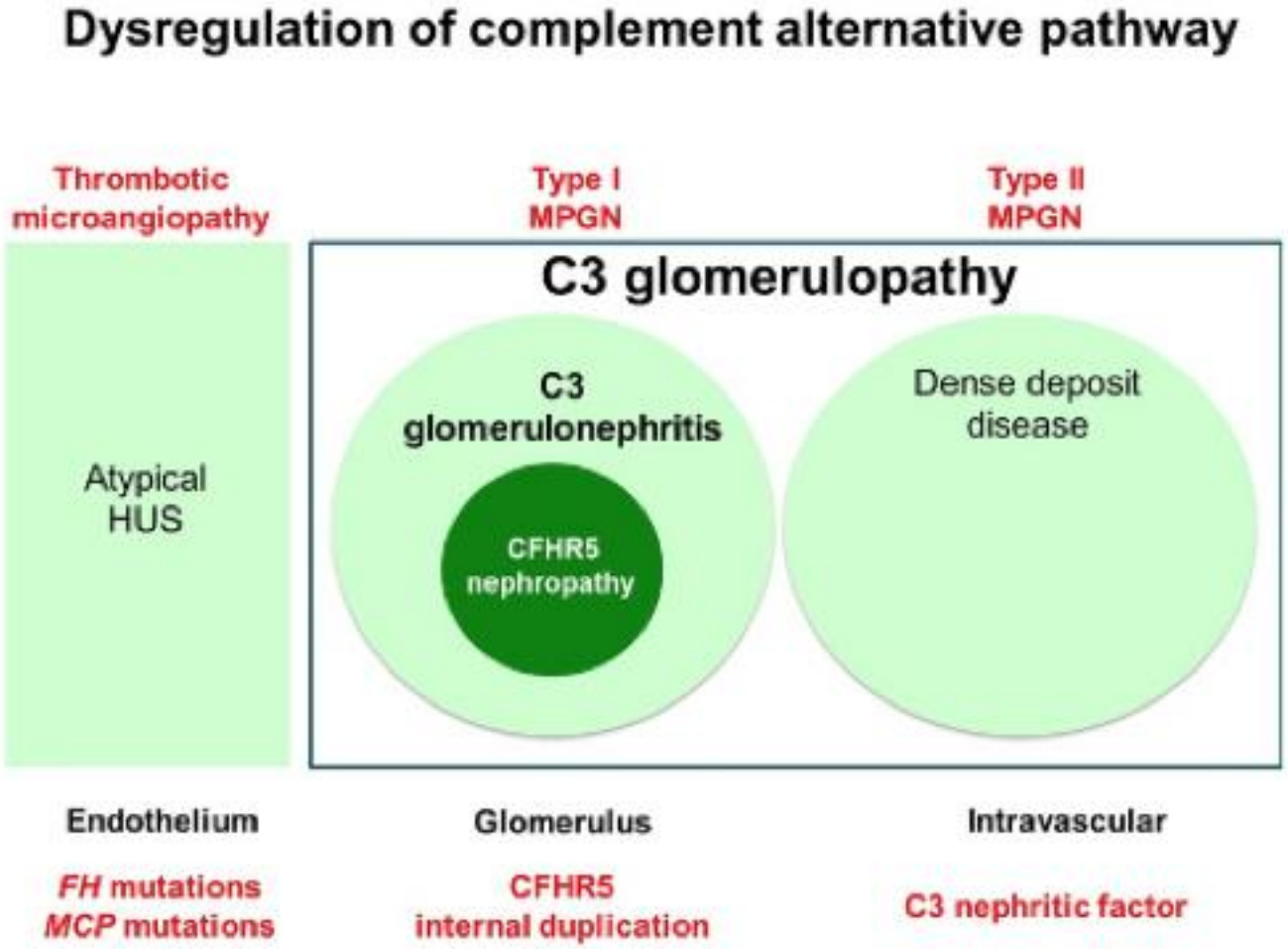
Disease	Associated Gene Mutations or Variations
Thrombotic Microangiopathy	
Atypical hemolytic uremic syndrome	Factor H, factor I, C3, factor B, membrane cofactor protein, CFHR1, CFHR3, thrombomodulin
Shiga toxin–associated hemolytic uremic syndrome	Membrane cofactor protein
Thrombotic thrombocytopenic purpura	Factor H
HELLP syndrome	Factor H, factor I, membrane cofactor protein
De novo thrombotic microangiopathy after renal transplantation	Factor H, factor I
Pre-eclampsia	Factor I, membrane cofactor protein
Hematologic stem cell transplant related	CFHR1, CFHR3
C3 Glomerulopathy	
C3 glomerulopathy	Factor H, C3, factor B, membrane cofactor protein, CFHR1, CFHR2, CFHR5
Dense-deposit disease	Factor H, C3, CFHR5
Immune Complex Glomerular Disease	
MPGN type I	Factor H, factor I
IgA nephropathy	CFHR1, CFHR3

Abbreviations: CFHR, complement factor H–related protein; HELLP, a syndrome of hemolysis, elevated liver enzymes, low platelets; Ig, immunoglobulin; MPGN, membranoproliferative glomerulonephritis.

Spettro delle malattie renali complemento-mediate

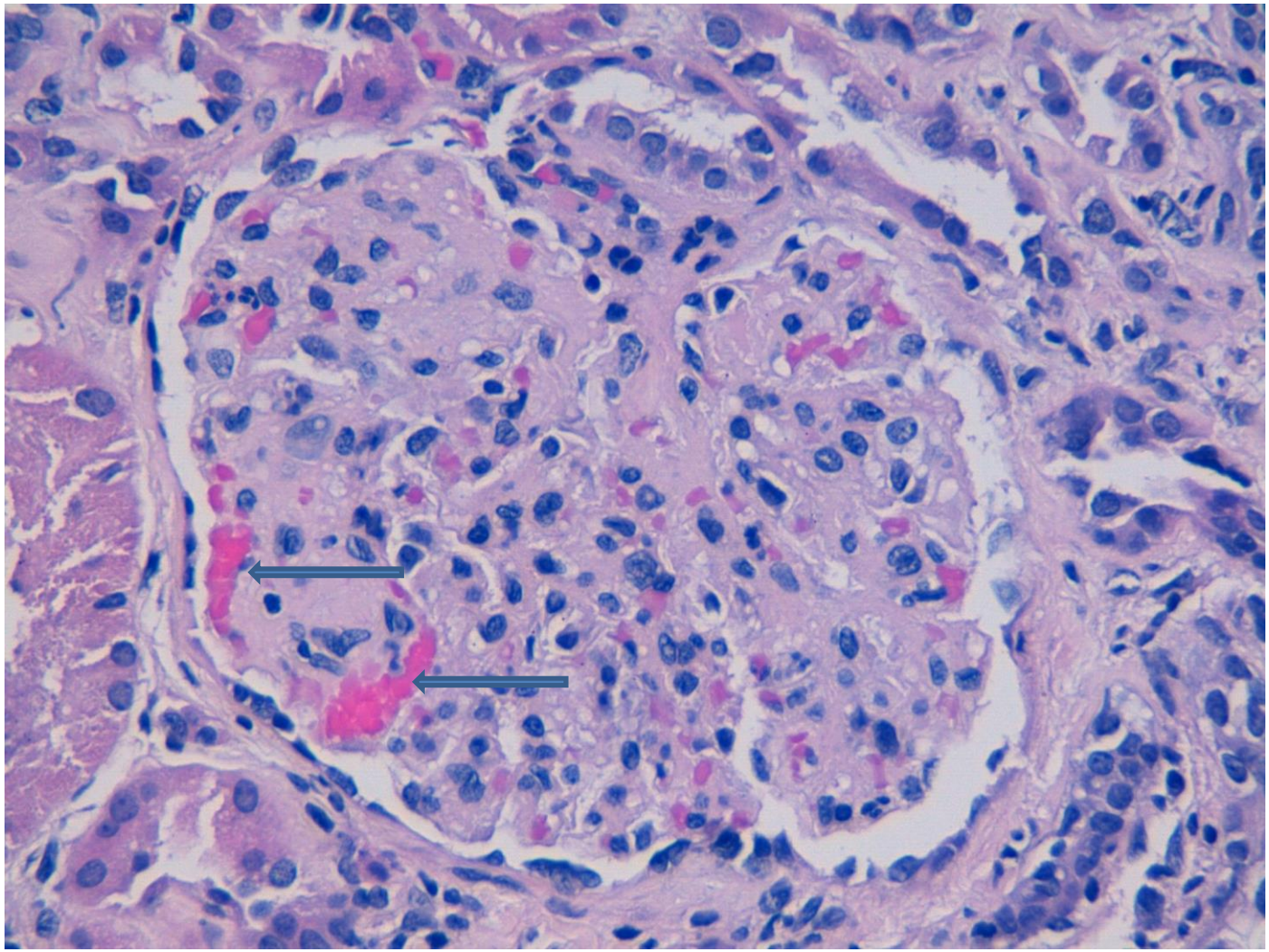
J M. Thurman Am J Kidney Dis. 2015;65(1):156-168

Spettro delle malattie renali complemento-mediate



P.Maxwell, London, UK ERA-EDTA 2012

Istologia renale in corso di aSEU



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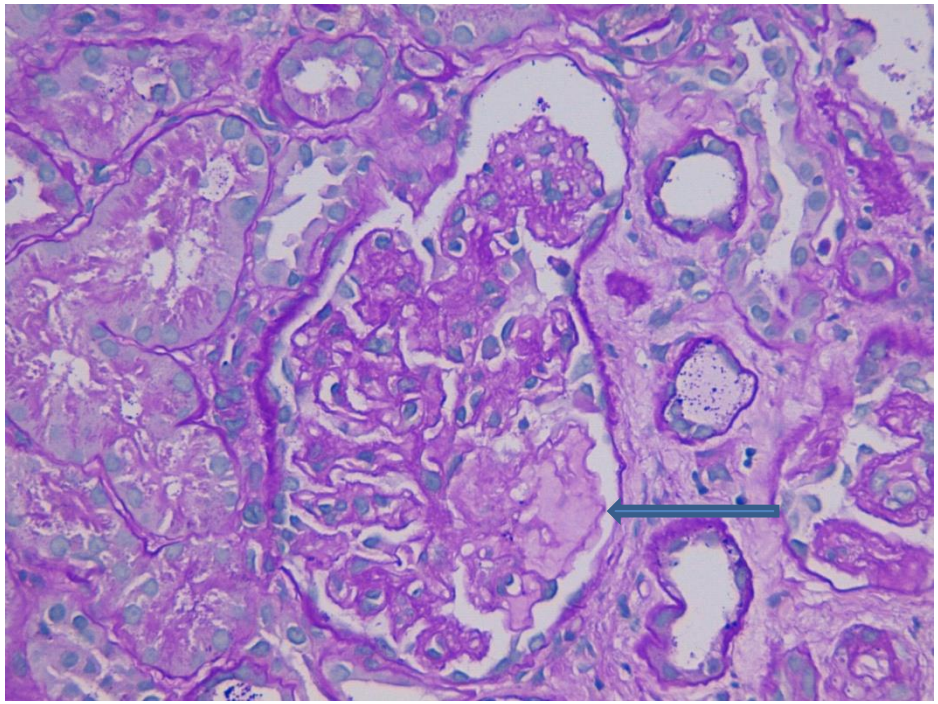
Istologia renale in corso di aSEU



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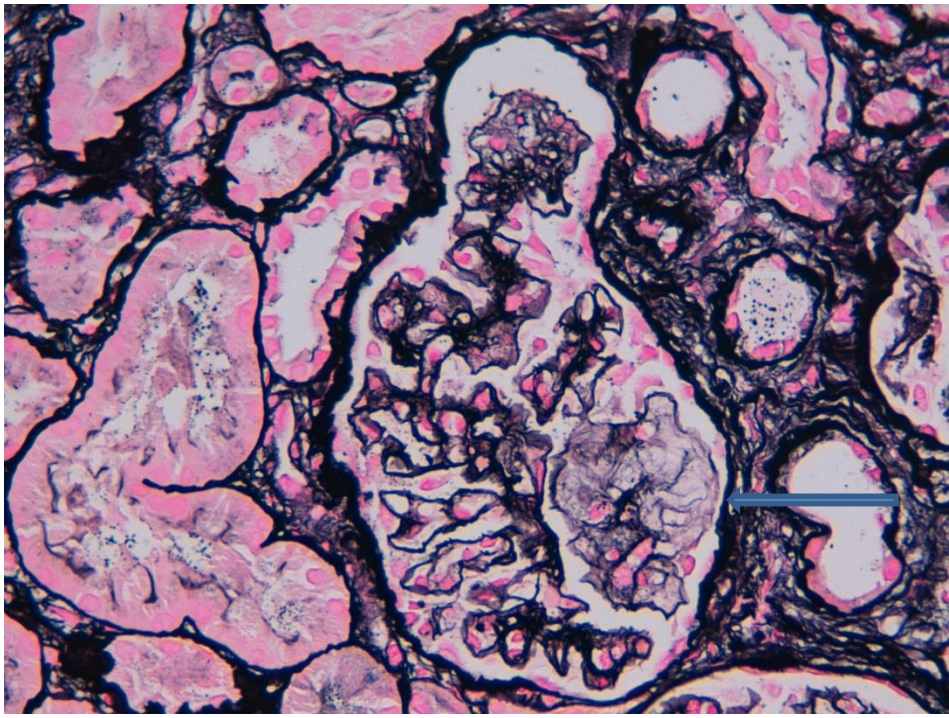

PASM 400x

aree di mesangiolisi

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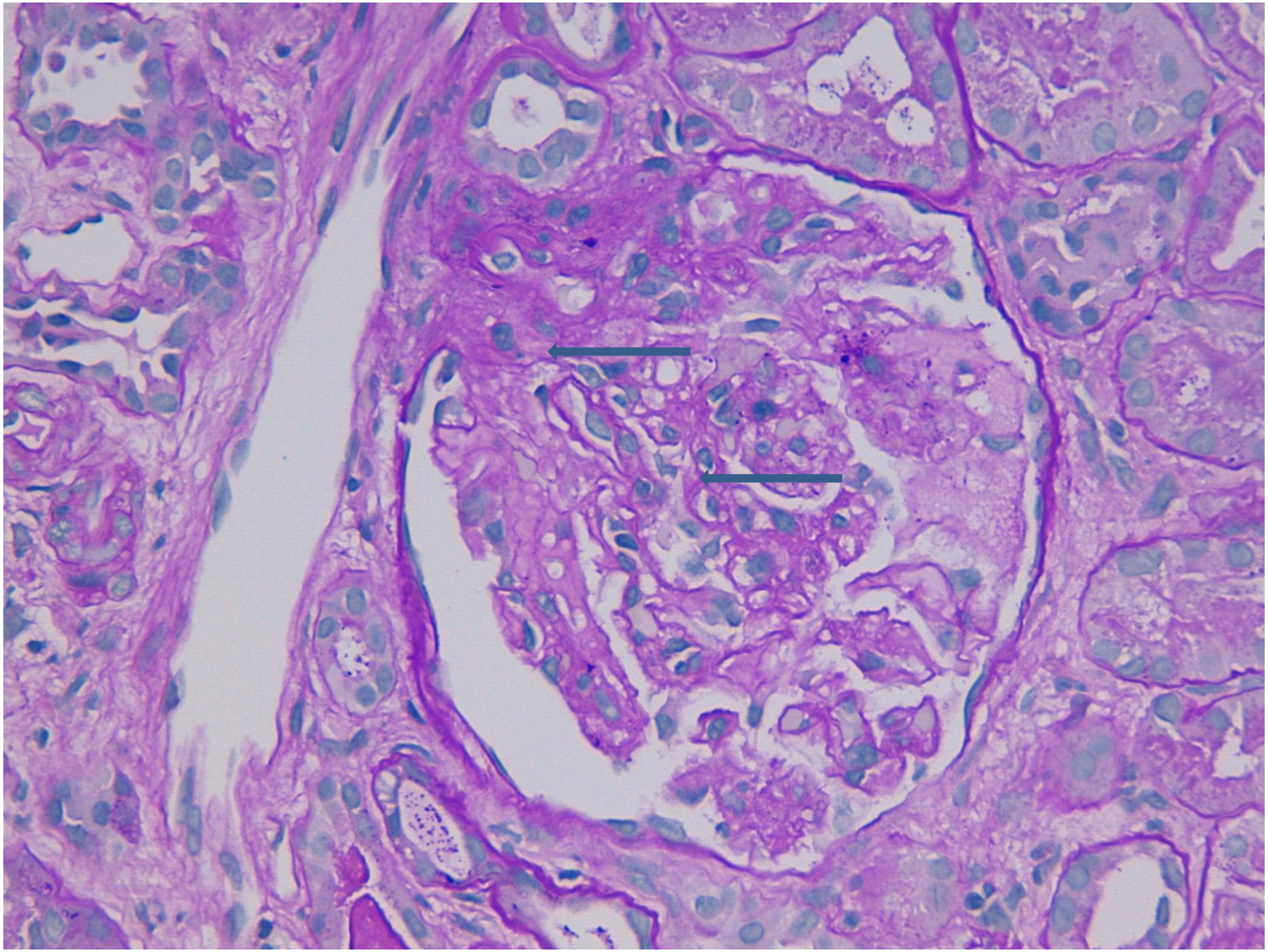
Istologia renale in corso di aSEU



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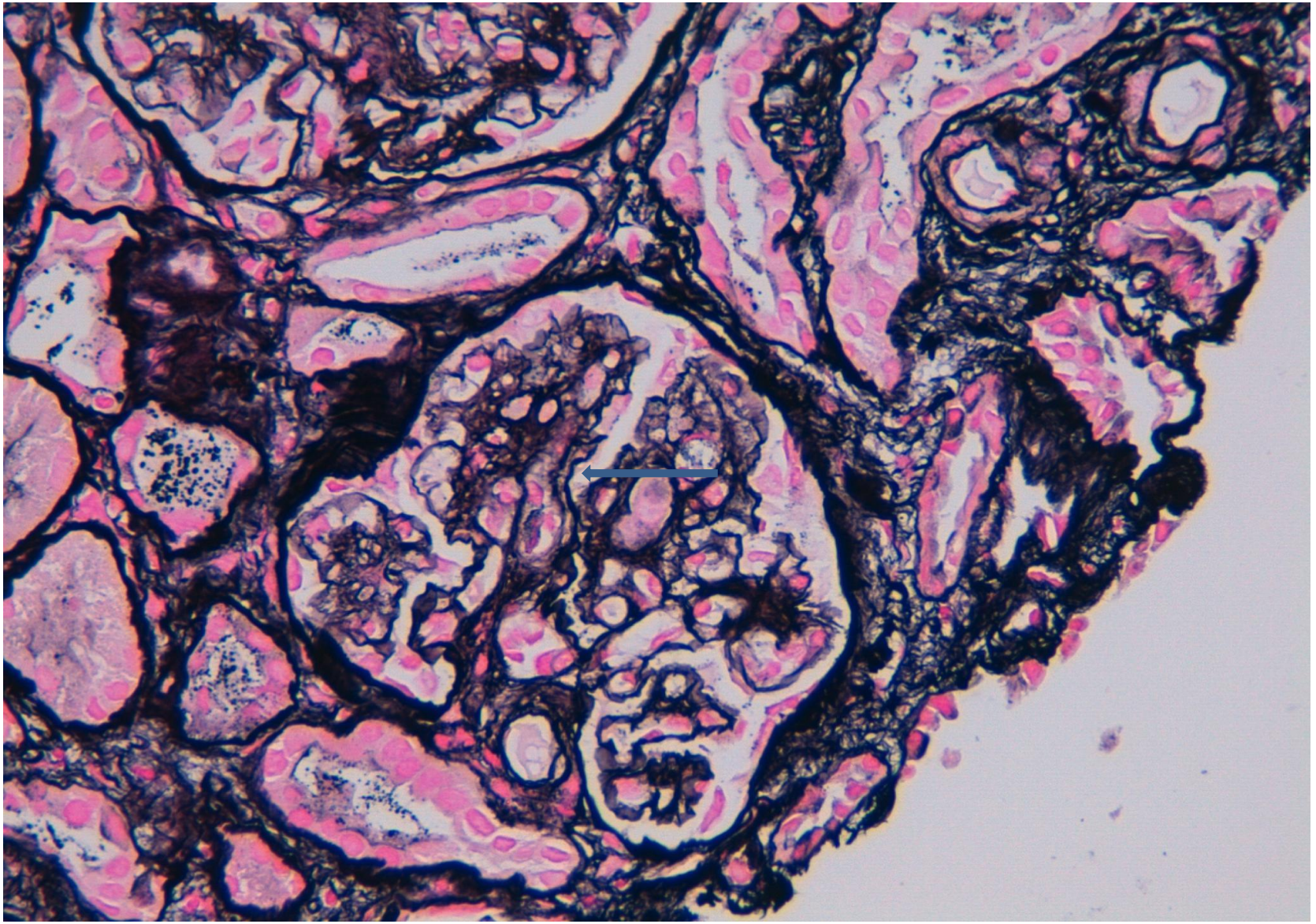
Istologia renale in corso di aSEU



PASM 400x

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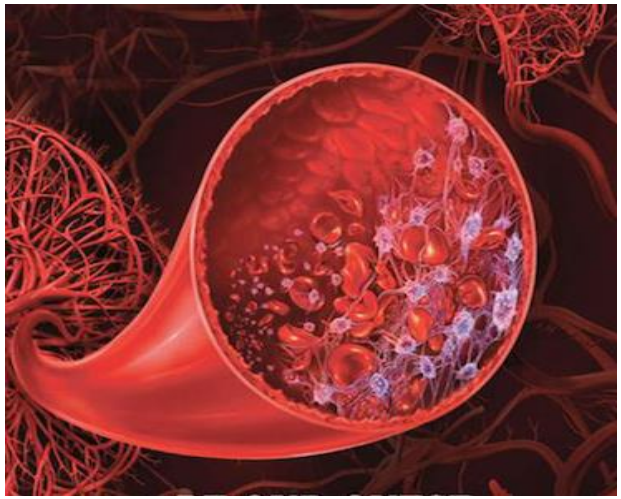
Diagnosi della Sindrome emolitico-uremica atipica (aSEU)



Diagnosi della Sindrome emolitico-uremica atipica (aSEU)

Valutazione iniziale di soggetti con SEU

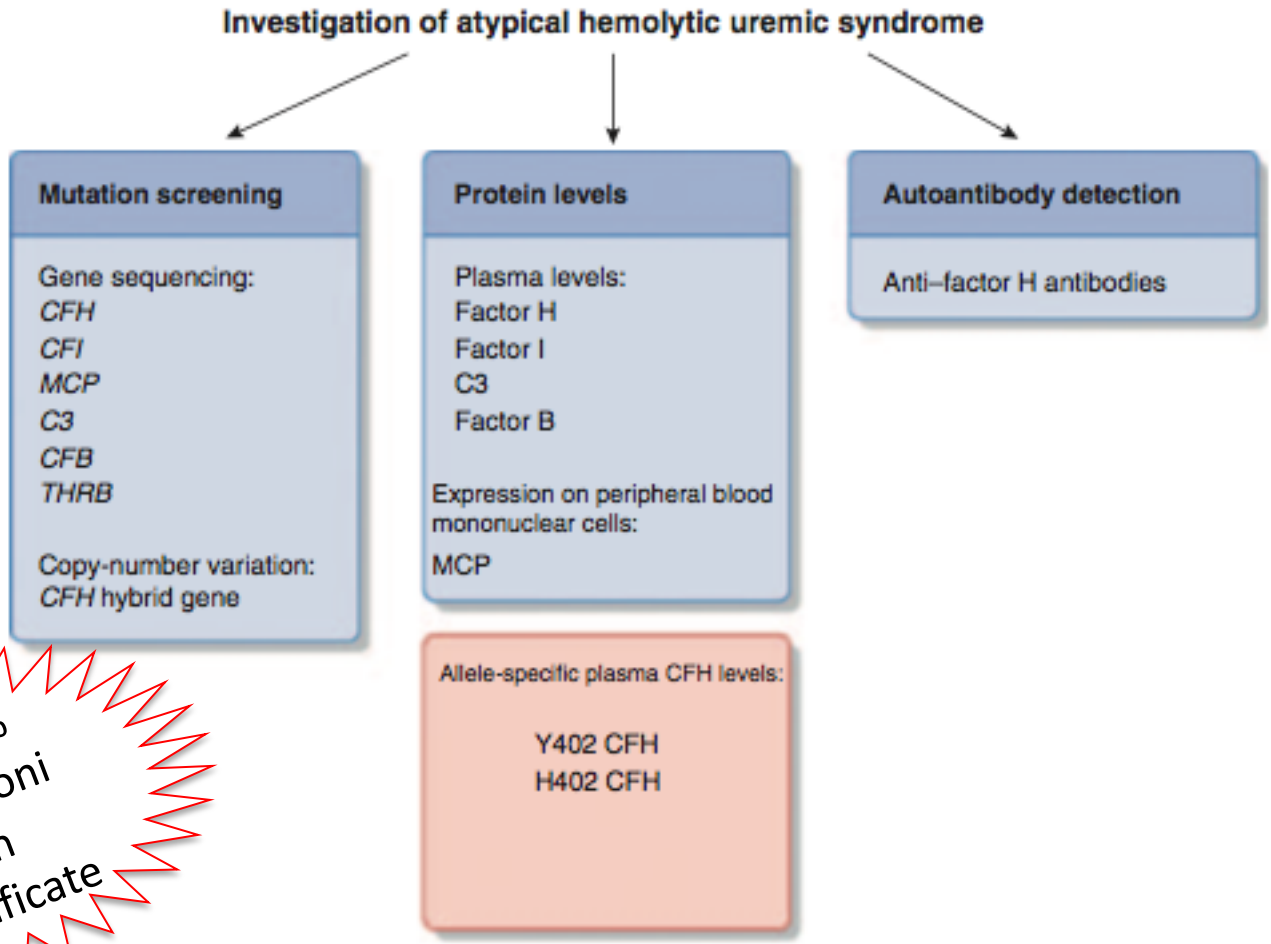
Infezione	Disfunzione d'organo	Alterazioni immunologiche
Coprocoltura o tampone rettale, ricerca Shiga-toxin	Esami funzione renale,esame urine	ANA,ANCA,ENA, LAC, AB anti fosfolipidi
HIV	Esami funzione epatica	Fattore reumatoide
Influenza	Enzimi pancreatici	
Emocolture		
Colture espettorato	Rx-torace	
Test per zoonosi	Ecotomografia renale	
ADAMTS13 attività plasmatica ±inibitori	Test gravidanza	Carenza di cobalamina
		-Omocisteina plasmatica e metionina -Acido metilmalonico urinario

Diagnosi della Sindrome emolitico-uremica atipica (aSEU)

Test del complemento in soggetti che presentano SEU

Autoanticorpi e carenze di proteine	Test attività sierica del complemento	Screening per le varianti genetiche e/o variazioni numero copie
FH autoanticorpi	C3	CFH
FI autoanticorpi	Funzione via alterna	CFI
FH Livelli	Attività della cascata complementare terminale	MCP
FB livelli		C3
FI livelli		CFB
CD46 su leucociti		CFHR1-5
		DGKE
		CNVs nella regione CFH-CFHR

Test di laboratorio nella aSEU



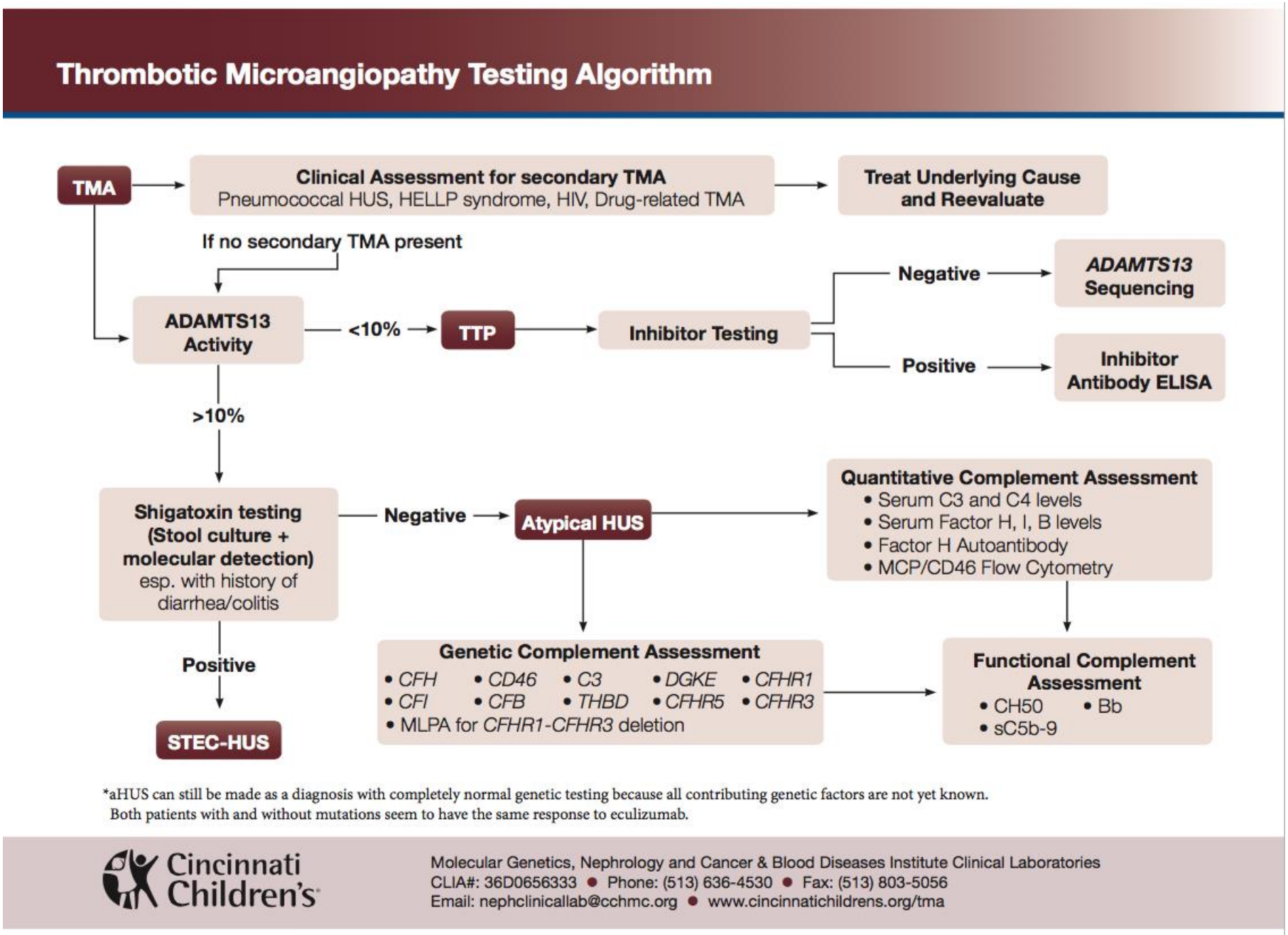
30-50% mutazioni non identificate

E. Goicoechea de Jorge.Kidney International (2010) **78,** 721–723

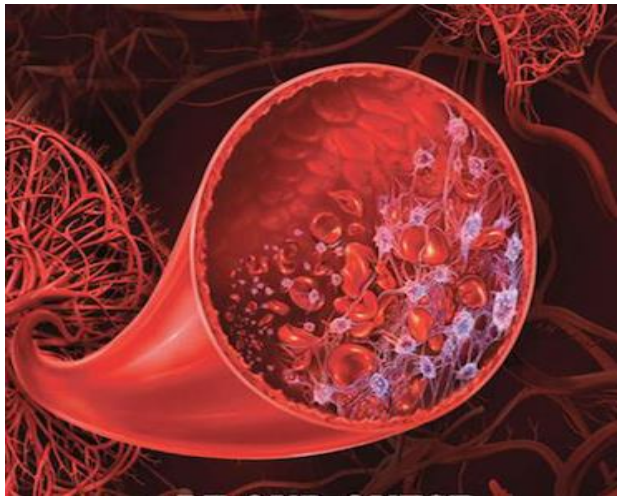
Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies British Journal of Haematology 2012

Clinical Practice Guidelines for the Management of Atypical Hemolytic Uremic Syndrome in Korea J Korean Med Sci 2016; 31: 1516-1528

Algoritmo diagnosi aSEU e TTP



Prognosi ed outcome della Sindrome emolitico-uremica atipica (aSEU)



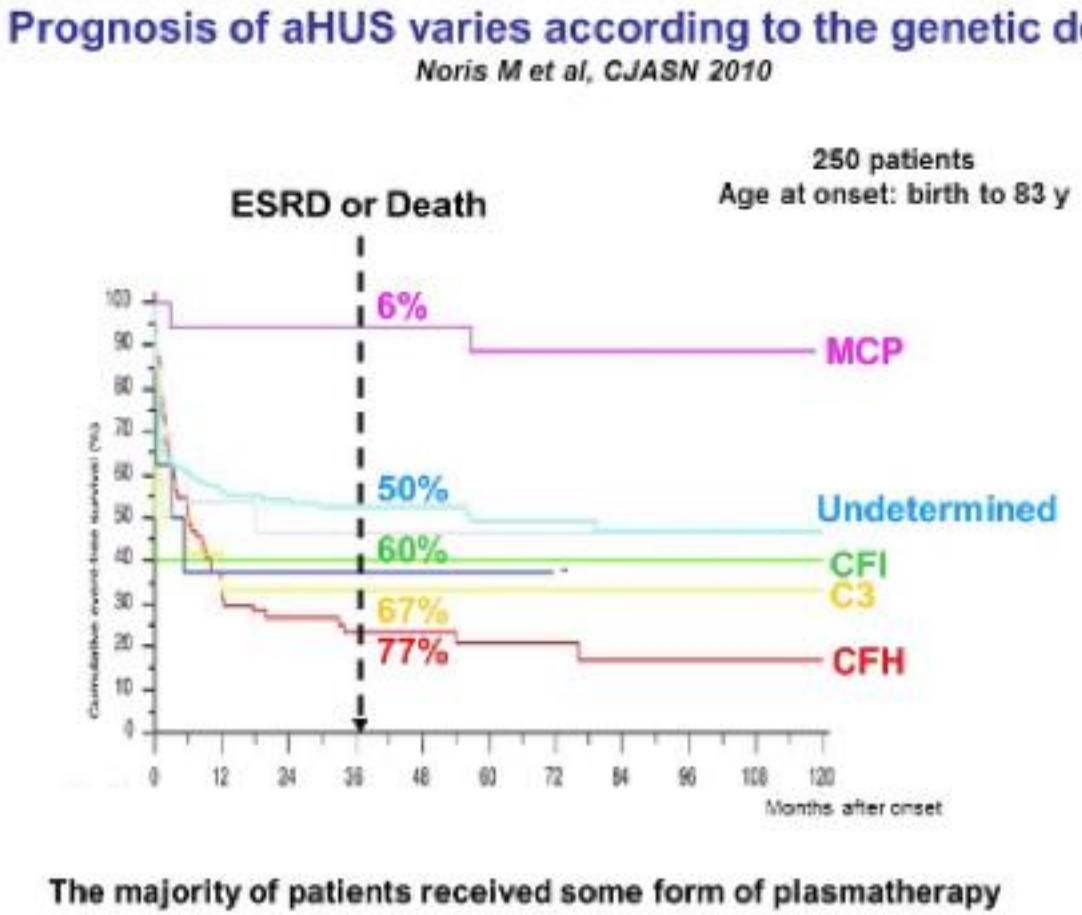
• Prognosi ed outcome della Sindrome emolitico-uremica atipica (aSEU)

- **80% dei pazienti aSEU ha prognosi peggiore rispetto a coloro affetti da STEC-SEU**
- **All'esordio, la maggior parte dei pazienti necessita di dialisi**
- **In era pre- Ab monoclonali anti-C5 , circa 50% non recuperava funzione renale**
- **Al primo episodio, maggiore mortalità nei bambini rispetto agli adulti**
- **A 5 anni dall'esordio, 48%dei bambini e 67% degli adulti muore o ha raggiunto ESRD**

Noris M, Remuzzi G. Am J Kidney Dis. 2015;66(2):359-375

Le anomalie genetiche individuali influenzano

- outcome a lungo termine
-fenotipo clinico
-risposta al trattamento



273 pazienti
International Registry of recurrent and familial HUS/TTP

Le anomalie genetiche individuali influenzano la prognosi

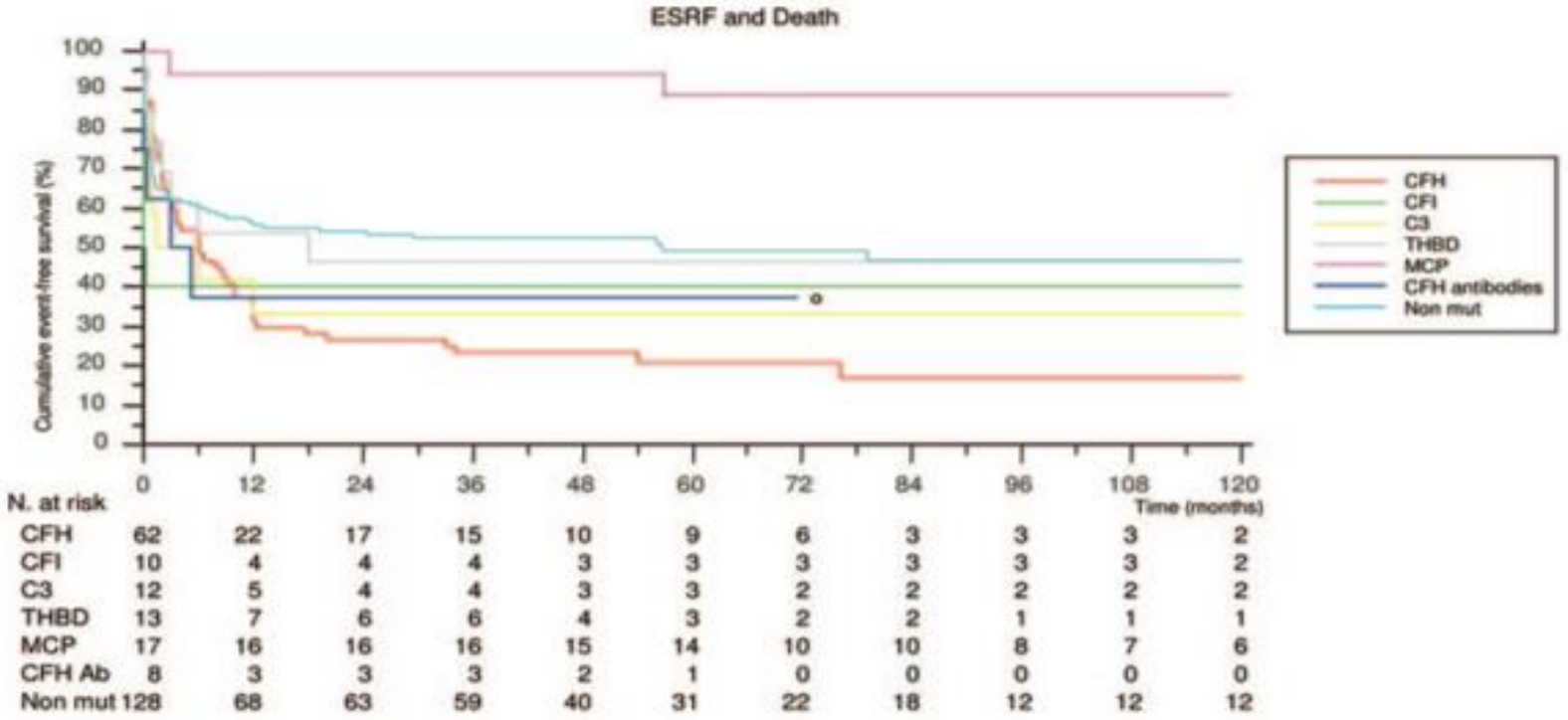
Table 4. Summary of the most relevant clinical findings

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%)

[a]Comparison between sporadic and familial forms: $P < 0.0001$.
[b]Comparison between children and adults: $P = 0.004$.
[c]Comparison between children and adults: $P < 0.0001$.
CR, complete remission; PR, partial remission.

Noris M. Clin J Am Soc Nephrol 5: 2010.

Le anomalie genetiche individuali influenzano la prognosi

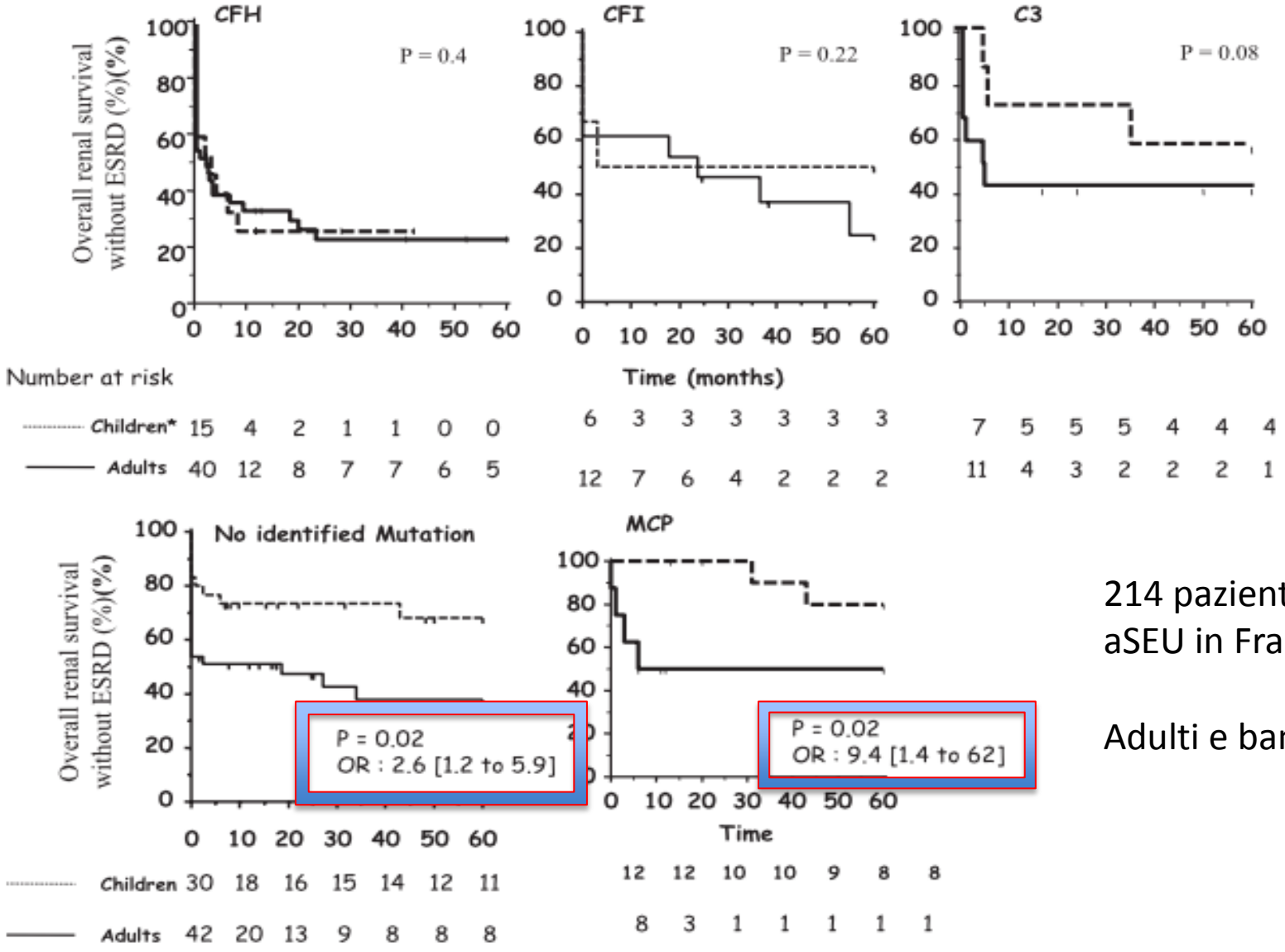


Comparison	HR	95% C.I.	P value
CFH vs MCP	13.55	3.29-57.79	<0.0001
CFH vs non mut	1.73	1.19-2.51	0.0032
CFI vs MCP	7.83	1.55-39.54	0.0028
C3 vs MCP	9.62	2.02-45.75	0.0006
THBD vs MCP	6.88	1.41-33.75	0.0066
CFH Ab vs MCP	8.49	1.61-44.69	0.0028
Non mut vs MCP	6.08	1.49-24.76	0.0037

Marina Noris et al

Clin J Am Soc Nephrol 5: 1–16, 2010.

Le anomalie genetiche individuali influenzano la prognosi



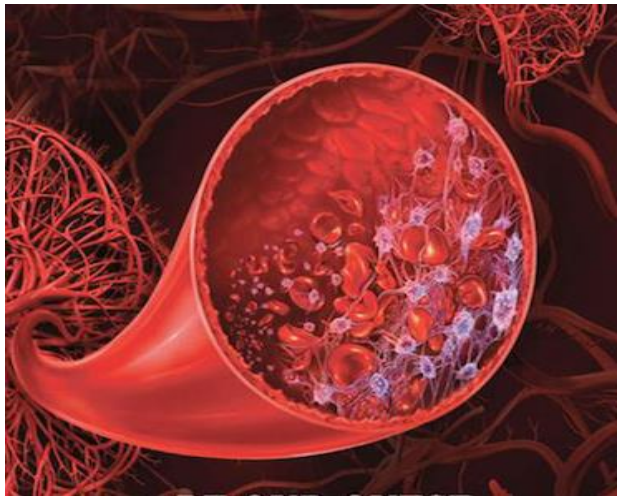
214 pazienti con aSEU in Francia

Adulti e bambini

Clin J Am Soc Nephrol 8: 554–562, April, 2013

Fremeaux-Bacchi et al.

Terapia della sindrome emolitico-uremica atipica (aSEU)



Terapia della sindrome emolitico-uremica atipica (aSEU)

Terapia di supporto

-trasfusioni di globuli rossi
-trasfusioni piastrine se sanguinamento attivo
-correzioni alterazioni elettroliti e fluidoterapia , se necessaria
-dialisi
-nutrizione

Terapia con plasma

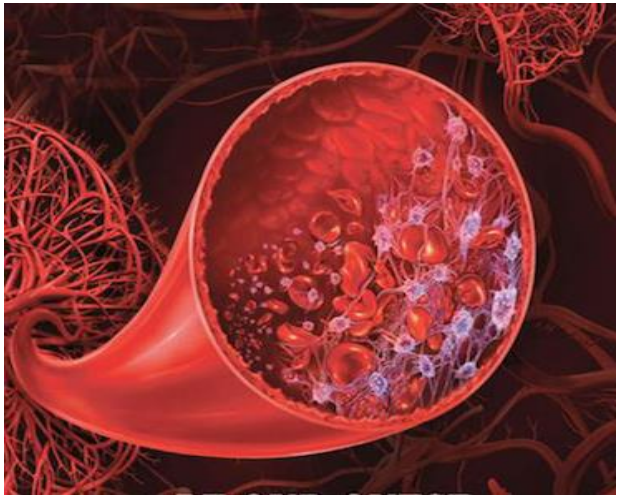
-plasma-exchange
-infusione di plasma

Trapianto

-rene
-rene e fegato

Farmaci

Eculizumab
Fattore H ricombinante
Trombomodulina ricombinante umana solubile



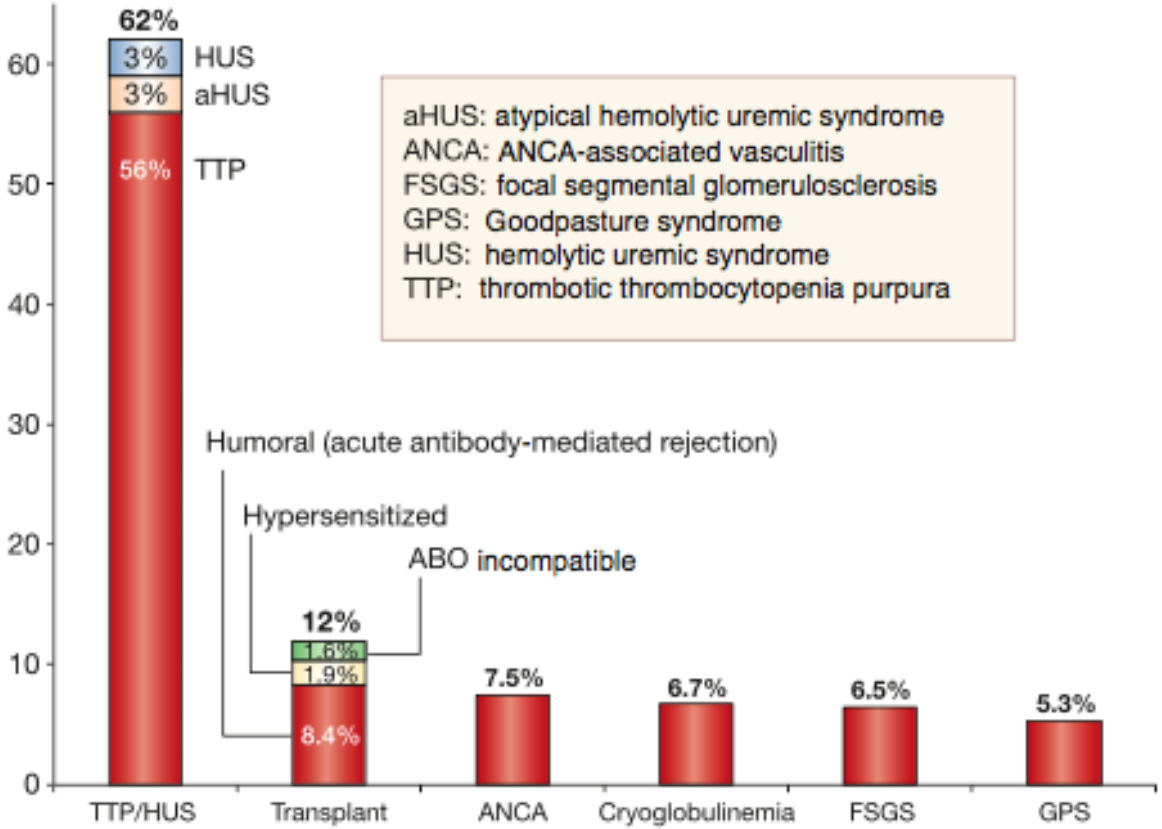


Figure 1 | The 6 most common renal indications for plasma exchange therapy in 2014. Created with data from Patriquin C, Clark WF. Canadian Apheresis Group 2014 plasma exchange data review: hematological, renal/collagen vascular, dermatological and transplant. Data review. Paper presented at: 35th Annual General Meeting of the Canadian Apheresis Group. September 18–20, 2015; Winnipeg, Manitoba.[9] ANCA, anti–neutrophil cytoplasm antibodies. Source: Canadian Apheresis Group.

W. F. Clark, et al Kidney International (2016)

Rischio di ricorrenza di aSEU su trapianto renale: correlazione con mutazioni genetiche

Table 1 | Characteristics of genetic mutations associated with aHUS and risk of recurrence after kidney transplantation without prevention or treatment.

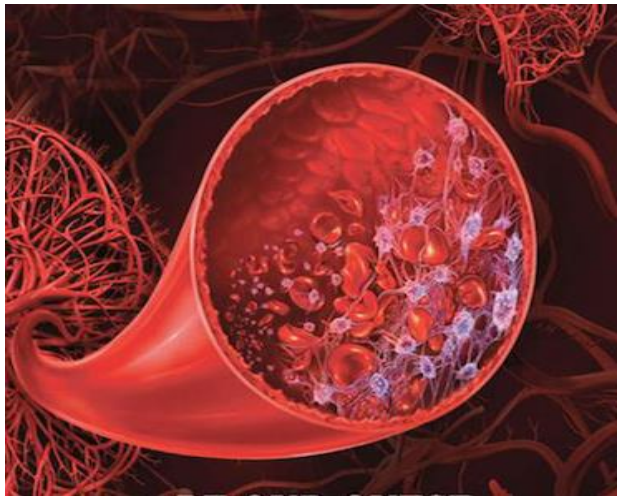
Mutation	aHUS incidence	Type of deficiency	C3 level	Risk of recurrence post-transplant
CFH	20–30%	70% Qualitative and 30% quantitative	Low in 30% (quantitative deficiency)	70–80%
MCP	10–15%	70% Qualitative and 30% quantitative	Low in 30% (quantitative deficiency)	Low (unless associated with other mutations)
CFI	5–10%	70% Qualitative and 30% quantitative	Low in 30% (quantitative deficiency)	70–80%
CFB	1–4%	–	Always low	100% (only 4 cases reported)
THBD	3–5%	–	Low in 50%	Unknown but probably very low
C3	2–10%	Majority are quantitative	Low in 80%	40%
Anti-CFH Abs	6%	N/A	Low in 40–60%	40–70% Depending on associated mutations
CFHR 1–5	Unknown	Usually qualitative	Normal unless it is associated with other mutations	Unknown
Combined mutations	10–12%	Variable	Variable	Variable

aHUS, atypical hemolytic uremic syndrome; C3, complement factor 3; CFH, complement factor-H; MCP, membrane co-factor protein; CFI, complement factor-I; CFB, complement factor B; THBD, thrombomodulin; CFHR, complement factor-H related proteins.

S. Alasfar www.frontiersin.org 2014 (1) 52:1-12

M.Salvadori Word J of Nephrol, 2013 (2)3

Ruolo del nefrologo



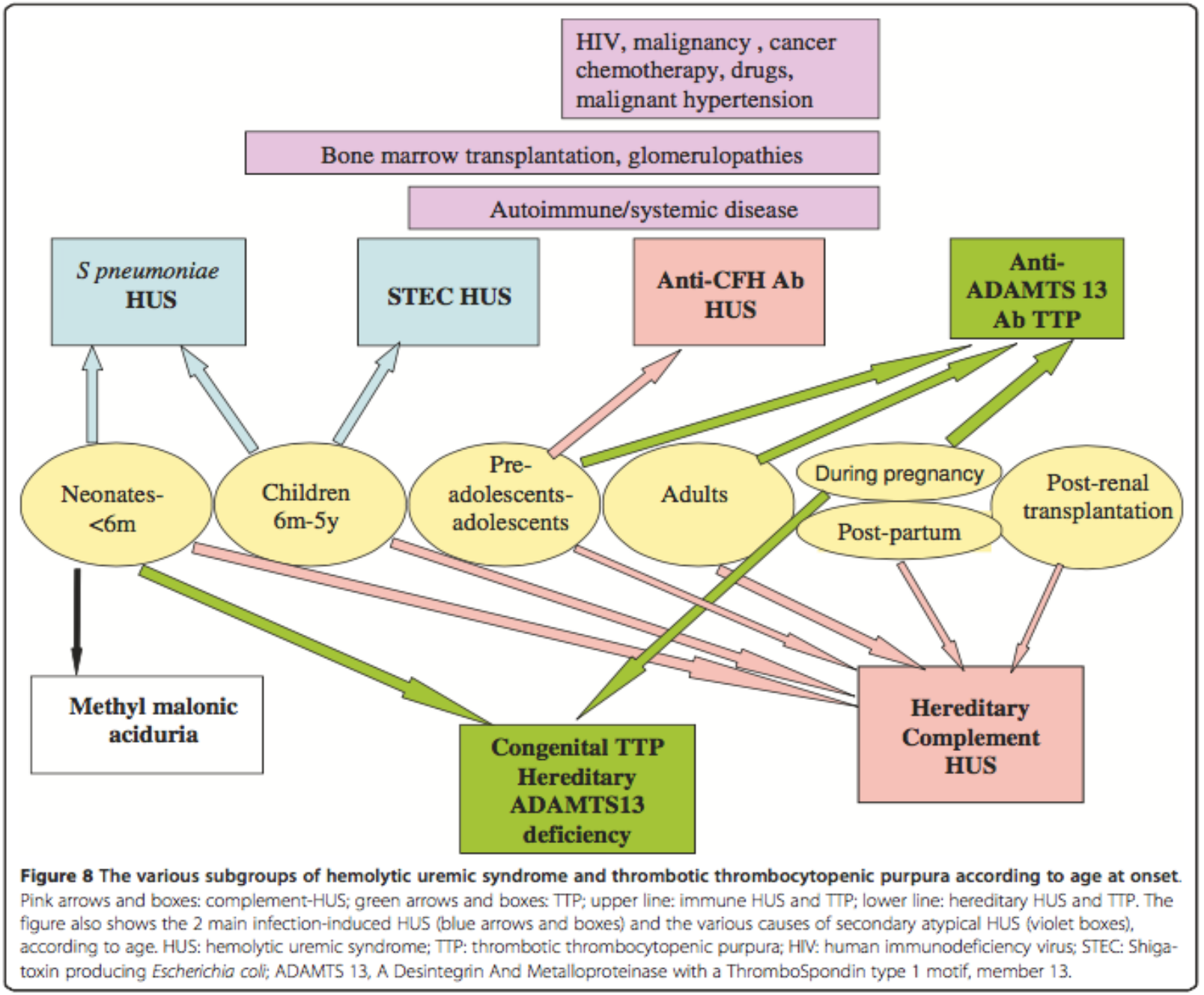


Figure 8 The various subgroups of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura according to age at onset. Pink arrows and boxes: complement-HUS; green arrows and boxes: TTP; upper line: immune HUS and TTP; lower line: hereditary HUS and TTP. The figure also shows the 2 main infection-induced HUS (blue arrows and boxes) and the various causes of secondary atypical HUS (violet boxes), according to age. HUS: hemolytic uremic syndrome; TTP: thrombotic thrombocytopenic purpura; HIV: human immunodeficiency virus; STEC: Shiga-toxin producing *Escherichia coli*; ADAMTS 13, A Desintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13.

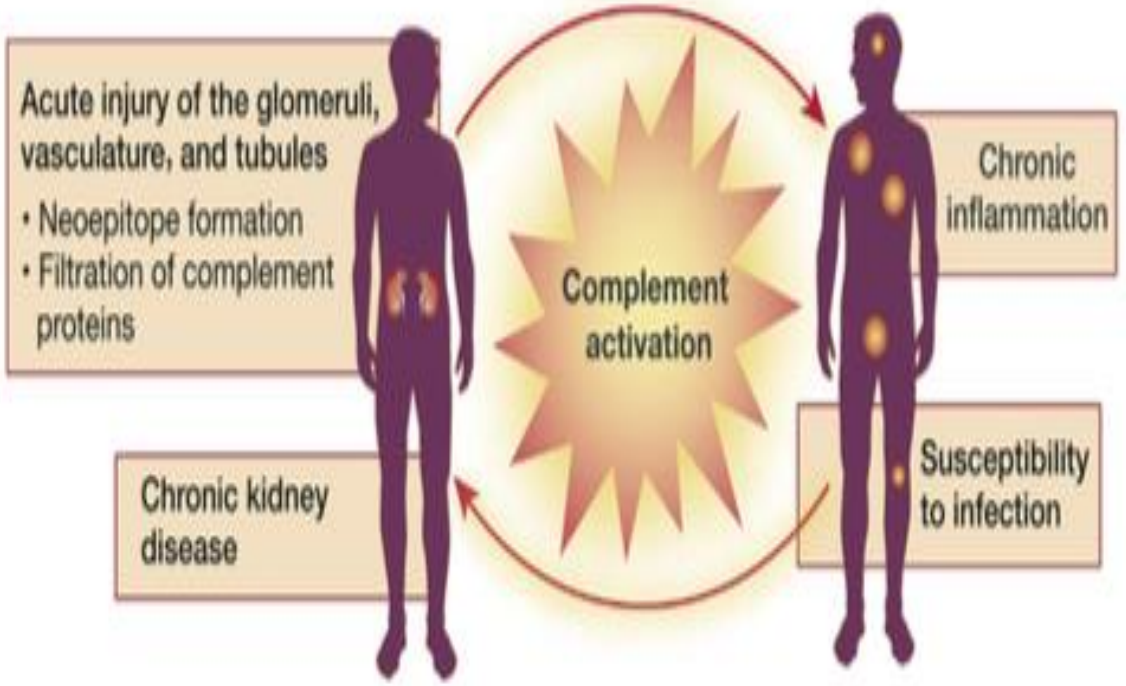
C.Loirat Orphanet J of Rare Disease 2011,6:60

Quadri clinici della Sindrome emolitico-uremica atipica (aSEU)

- Esordio subdolo
- Astenia, malessere, inappetenza, vomito
- Ipertensione arteriosa, insufficienza cardiaca, IMA [20%]
- Oliguria, ematuria, edema, insufficienza renale
- 59% dei bambini e 81% degli adulti richiede dialisi alla presentazione
- Irritabilità, convulsioni, diplopia, emiparesi, stupor, coma [10%]
- Diarrea /gastroenterite [80% pz pediatrici, 23-50% pz adulti]

Noris M et al. Clin J Am Soc Nephrol 2010,5:1844-1859
Fremeaux-Bacchi V. Clin J Am Soc Nephrol 2013,8:554-562

Prevenzione della malattia renale cronica



Il sistema del complemento e le malattie renali

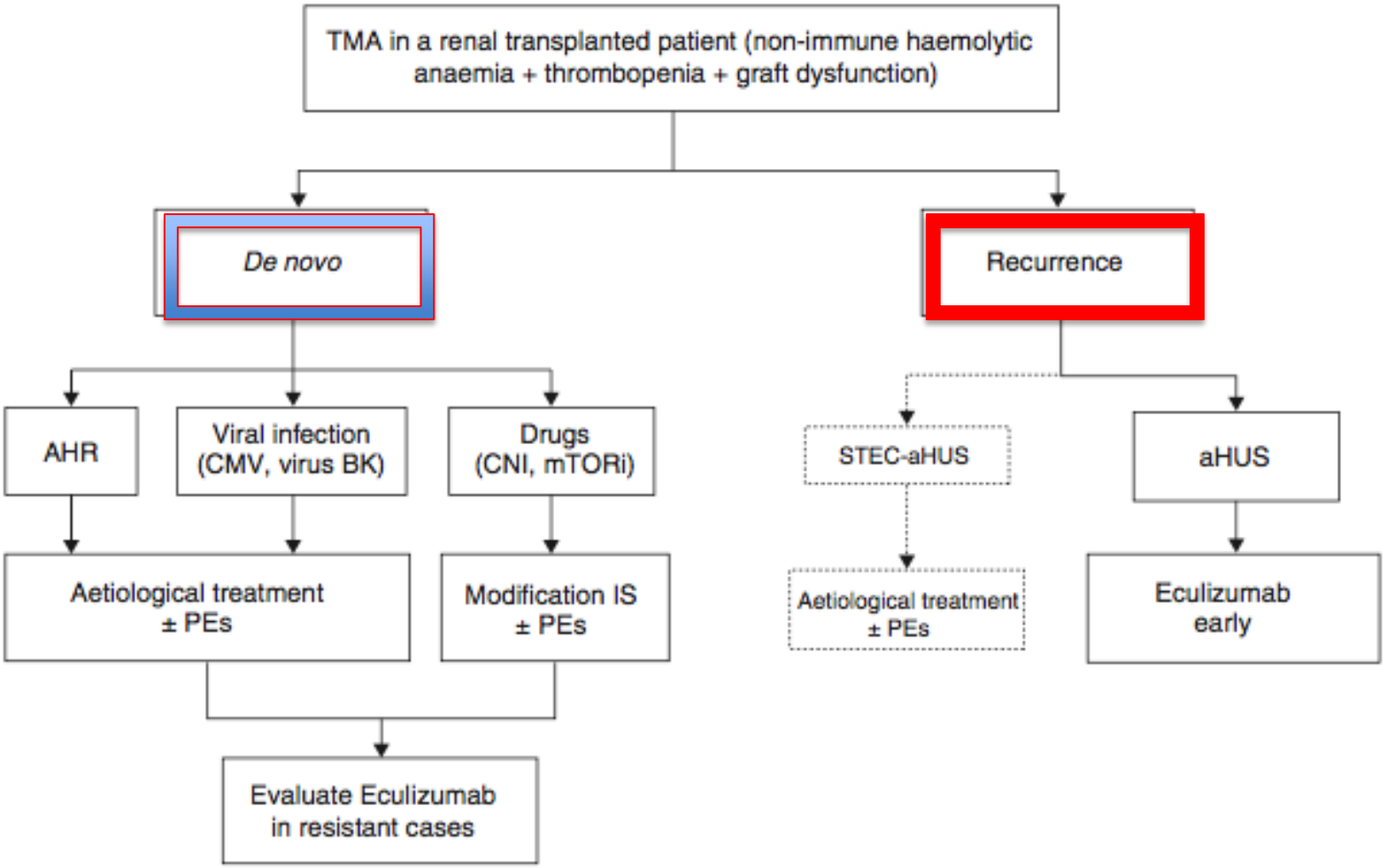
J. M. Thurman, M Le Quintrec Kidney International (2016) 90, 746–752

Trapianto renale e sindrome emolitico-uremica

◆Danno da ischemia-riperfusione (*delayed graft function*)
Danno endoteliale>ridotto CFH>attivazione via alterna del complemento>incremento C5b-9

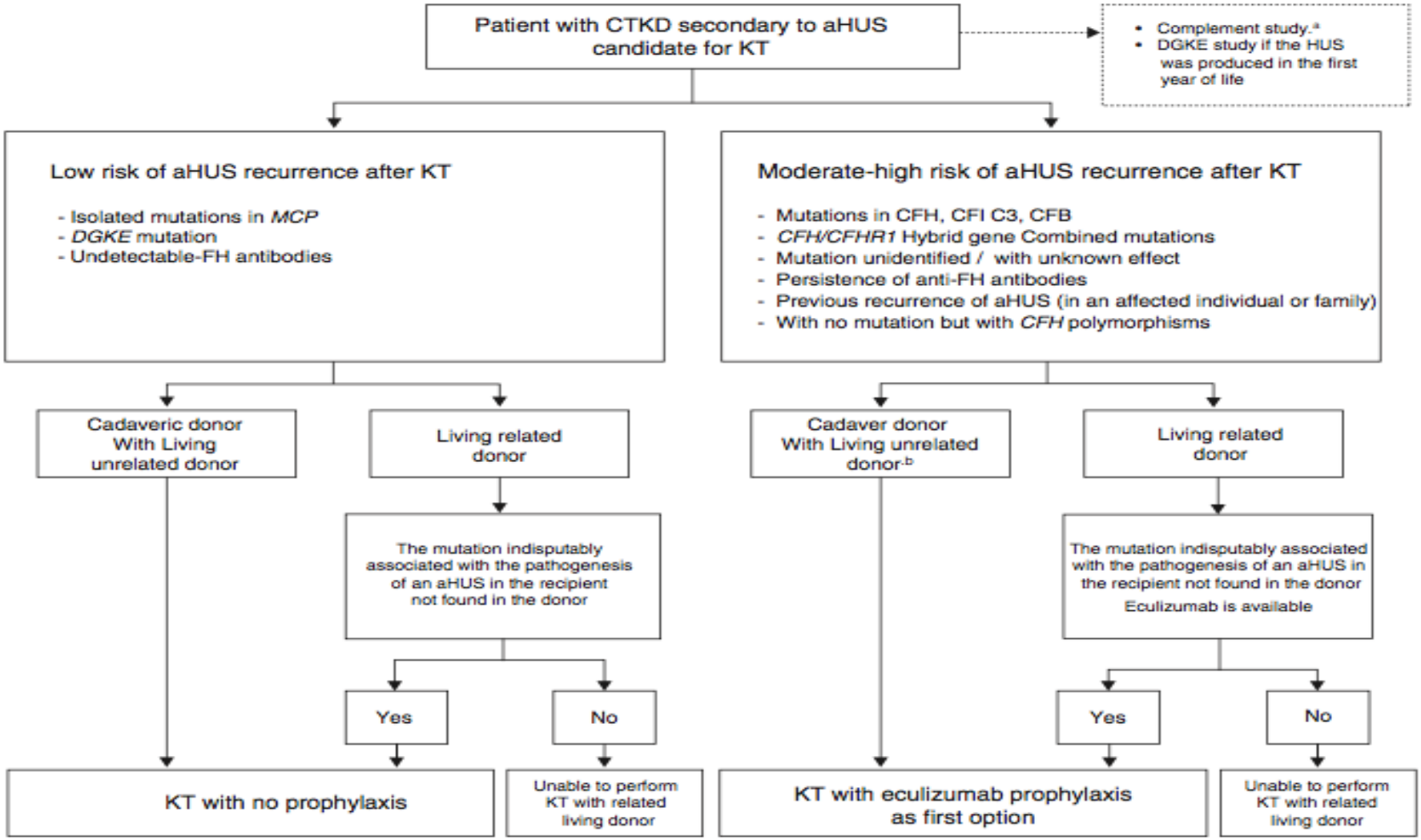
◆Infezioni
◆Uso di farmaci immunosoppressori
◆Rigetto

Trapianto renale e sindrome emolitico-uremica



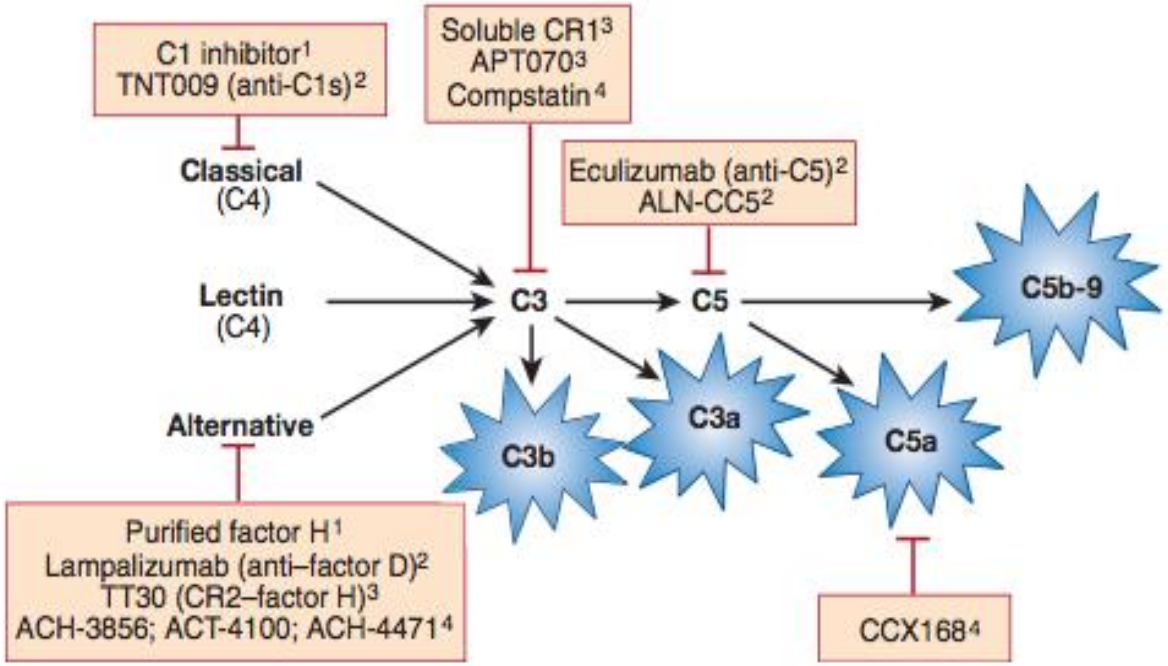
J.M. Campistol. Nefrologia. 2015;35(5):421–447

Trapianto renale e sindrome emolitico-uremica: Raccomandazioni su trattamento



J.M. Campistol. Nefrologia. 2015;35(5):421–447

Trapianto renale e sindrome emolitico-uremica: Farmaci che agiscono sulla cascata del complemento



J M Thurman Kidney International (2016) 90, 746–752;

In conclusione

✓ *……the earlier diagnosed and treated, the better…*

By Chantal Loirat and Veronique Fremeaux-Bacchi

✓ *Anche se veramente rara la aSEU può fornire un ottimo modello clinico e sperimentale per le malattie del complemento e la ricerca di nuovi farmaci*

✓ *La diagnosi della/e aSEU richiede un approccio multidisciplinare, è molto complessa e questo indica che la nostra conoscenza su questa patologia rimane ancora incompleta*


Grazie a Dr.ssa Elisa Ricci
Grazie a Fabrizio Boila
per le animazioni
Grazie a voi tutti per la attenzione!