GIOVEDÌ 30 MAGGIO 2024

15,00 – 16,30 SALA LEVANTE/PONENTE

LE DIAGNOSI VINCENTI

Moderatori: Biagio Epifani – Luciano D'Angelo

- Imprevedibilità della aTTP: un'emergenza clinica — *Luciano D'Angelo*

  relazione con il contributo non condizionante di Sanofi
- Le aritmie maggiori da tossici — *Paola Noto*
- Sindrome Emolitica Uremica acquisita — *Giulio Ricciuto*

LA SEUA (aHUS)

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XIII congresso nazionale simeu GENOVA 30 MAG - 1 GIU 2024

Diagnosi vincenti

dal greco διάγνωσις, da δια + γιγνώσκω, cioè riconoscere attraverso

Contesto (Dan Sandberg, BEEM 2014)

Emergency Medicine is the most interesting 15 minutes of every other specialty. We work

1. ***in a different environment,***
2. ***in different hours***
3. ***and with different patients more than any other specialty.***

Our motto is <u>Anyone, anything, anytime</u>.

While other doctors dwell on the question What does this patient have? (i.e., What's the diagnosis?), emergency physicians are constantly thinking

1. ***What does this patient need?***
2. ***Now?***
3. ***In 5 minutes?***
4. ***In two hours?***

Contesto

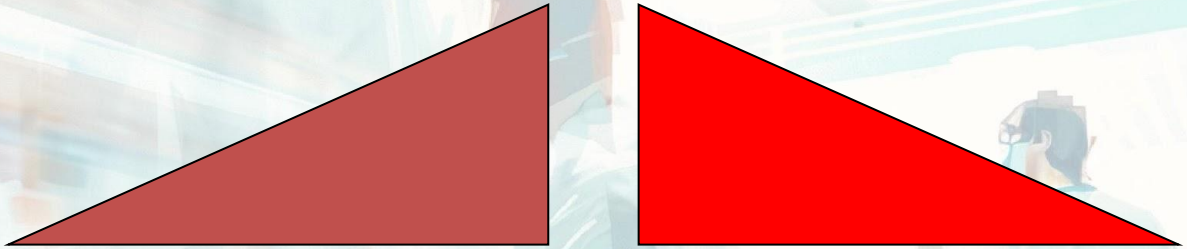
Diverso ed unico modo di agire nei confronti di pazienti quasi sempre

1. **sconosciuti**
2. **in gran numero contemporaneo**

che giungono in Pronto Soccorso

1. **con sintomi spesso aspecifici o iniziali e**
2. **con presentazioni talora insolite di malattie comuni**
3. **o con sintomi anche classici ma di malattie rare**

CONSUETO ITER DIAGNOSTICO-TERAPEUTICO



Raccolta Informazioni

Pensiero raziocinante

Intervento Terapeutico

Fare

ITER INTEGRATO IN MEDICINA DI URGENZA ***TIME IS LIFE***

APPROCCIO "TERAGNOSTICO" per ALGORITMI

tempo

contengono aspetti diagnostico-terapeutici contemporanei tra loro e sequenziali tesi a

1. **valutare e trattare la gravità della condizione di accesso sulla base dei parametri vitali,**
2. **stratificare il rischio correlato grazie all'applicazione di scores clinici oltre che della clinical gestalt**
3. **raggiungere la stabilità clinica mediante i trattamenti di maggiore evidenza nella migliore accuratezza diagnostica possibile,**


LEADERSHIP
SUCCESS
TEAMWORK


Together
Everyone
Achieves
More


TRUST
PARTNERSHIP
SHARE
TEAMWORK
HARMONIZE
NETWORK
COLLABORATE
SUPPORT
KNOWING


SKILLS
COMMUNICATION
POWER
SUPPORT
LEADERSHIP
COMPETENCE
TEAMWORK
RESPONSIBILITY

Indispensabile per essere **vincenti** in Pronto Soccorso, specie per le patologie tempo-dipendenti, è il ***lavorare in team con gli specialisti di altre discipline e con le altre professioni sanitarie***,
con il **medico d'emergenza e urgenza a fungere da team leader** coagulando intorno a sé gli apporti tecnici e culturali degli altri operatori
con il fine di **garantire rapidamente il miglior percorso** al paziente affetto da uno stato morboso evidentemente pericoloso per la vita.
Tale stretta collaborazione, poi, si fa ancora più continua nei reparti di **Medicina d'Urgenza e Terapia Sub Intensiva** dove spesso i pazienti più complessi vengono ricoverati, permettendo così una **crescita culturale globale** e la creazione di un **clima lavorativo ideale** per la produzione di *percorsi diagnostico terapeutici assistenziali condivisi e sempre aggiornati alle migliori pratiche cliniche esistenti*

H&S modello vincente per migliorare prognosi pazienti e identificare precocemente numero vero dei pazienti affetti

Centro di Riferimento a disposizione nei tempi compatibili con quelli richiesti dalla malattia, armonizzando i percorsi di tutti i centri satelliti e curandone la formazione degli operatori.

PS = FMC di tante patologie anche rare tra le quali le ***Microangiopatie Trombotiche***, alcune forme delle quali sono classificabili come **tempo-dipendenti** per l'alta mortalità ed esiti anche gravi se non correttamente diagnosticate e trattate all'esordio, ad attuale verosimile sottostima

MICROANGIOPATIE TROMBOTICHE (TMA)

gruppo eterogeneo di patologie caratterizzate dalla concomitanza di

a. **anemia emolitica microangiopatica non autoimmune** secondaria a frammentazione eritrocitaria meccanica intravascolare (Test di Coombs negativo)
b. **piastrinopenia da consumo** da aumentata aggregazione intravascolare (**microangiopathic hemolytic anemia and thrombocytopenia, MAHAT**) e formazione di coaguli nei piccoli vasi (capillari e arteriole),
c. **con conseguente ischemia variabile a carico di organi vitali** (prevalentemente encefalo, cuore e reni), ma anche a polmoni, occhio, intestino, fino a causare insufficienza d'organo terminale.
d. **Esordio spesso subdolo ma evoluzione**, ove non riconosciute e trattate immediatamente, **rapidamente ingravescente con elevata mortalità e morbilità**.

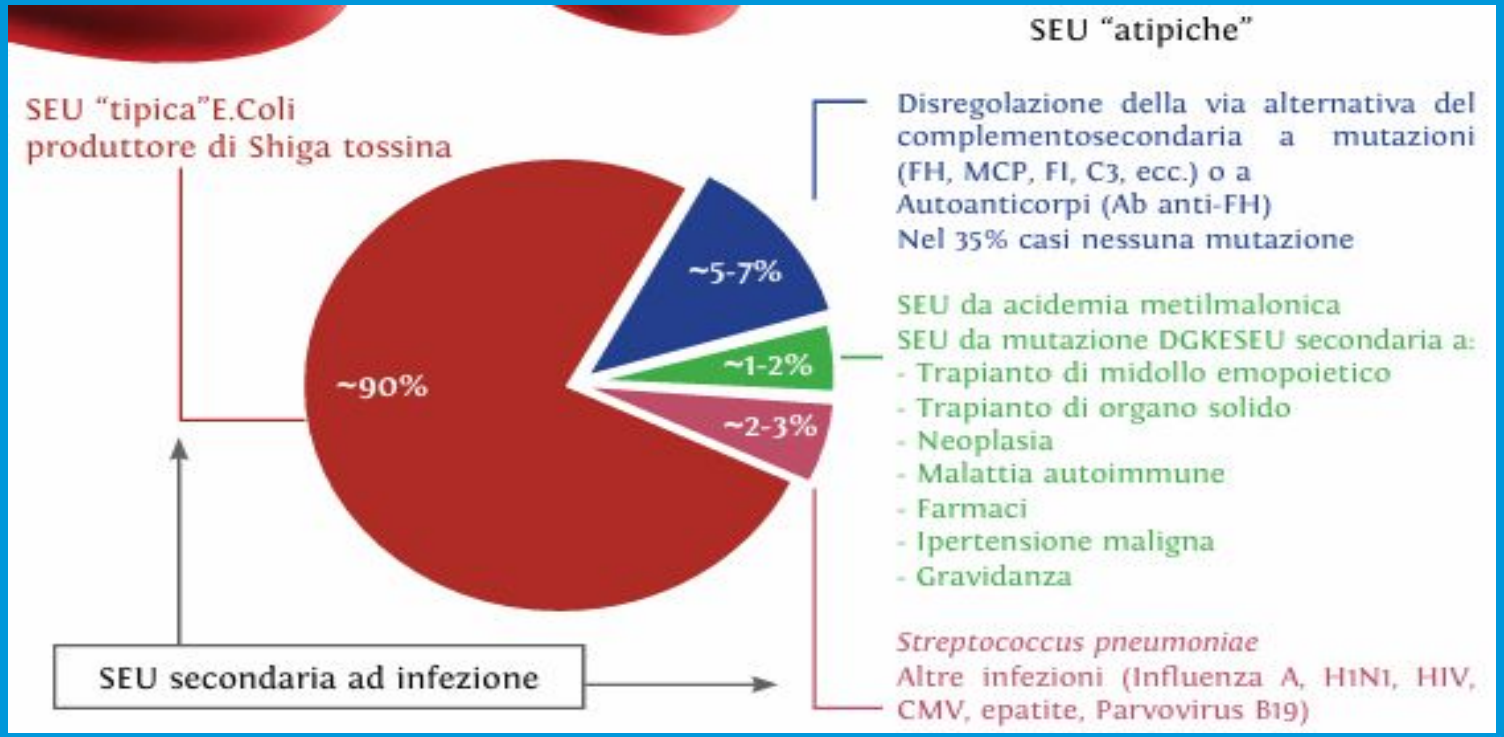
Tabella 1.1. Classificazione delle microangiopatie trombotiche.

MAT primarie
• PTT
• SEU
• DITMA
• Rari disordini ereditari di proteine regolatorie della coagulazione (TM; plasminogeno; DGKE)
• Rari disordini ereditari del metabolismo della vitamina B12 (mutazione del gene MMACHC)
Condizioni morbose che possono complicarsi con MAT secondarie
• Sindromi gravidiche: preeclampsia grave, eclampsia, sindrome HELLP
• CID
• Infezioni sistemiche gravi
• Ipertensione maligna
• Neoplasie maligne in stadio avanzato
• MAT secondarie a trapianto di organi solidi o cellule emopoietiche (conseguenza di terapie o in corso di rigetto acuto)
• Malattie immunoreumatologiche (CAPS, LES, SSc)

CAPS: sindrome da anticorpi anti-fosfolipidi catastrofica; CID: coagulazione intravascolare disseminata; DGKE: *diacylglycerol kinase epsilon*; DITMA: *drug-induced* TMA; HELLP: *hemolysis, elevated liver enzymes and low platelet count*; LES: lupus eritematoso sistemico; MAT: microangiopatie trombotiche; MMACHC: *methylmalonic aciduria and homocystinuria type C*; PTT: porpora trombotica trombocitopenica; SEU: sindrome emolitico-uremica; SSc: sclerosi sistemica; TM: trombomodulina.

Le forme primarie sono causate da uno specifico meccanismo patogenetico (ereditario o acquisito) e, pertanto, richiedono un trattamento eziologico specifico.

Le forme secondarie sono il risultato di disordini sistemici complicati da uno stato di infiammazione sistemica con danno endoteliale. In questi casi, il trattamento deve mirare alla malattia di base.



SINDROME	gruppo eterogeneo condizioni
EMOLITICO	presenza di anemia emolitica
UREMICA	alta incidenza di IR anche subito ES

Atypical hemolytic–uremic syndrome

Genetic, chronic, and progressive inflammatory disease that affects patients of **all ages**.

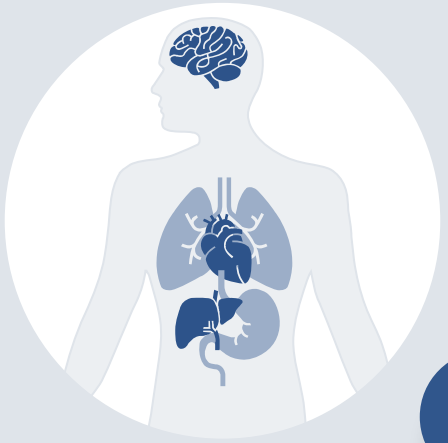
This syndrome is caused by **defects in regulation of the complement system**.

These defects are **inherited, acquired, or both**, and they result in ***chronic, uncontrolled activation of the complement system which leads to platelet, leukocyte, and endothelial-cell activation and systemic thrombotic microangiopathy***.

Affected patients have a ***lifelong risk of systemic clinical complications*** *of thrombotic microangiopathy, including damage to multiple organ systems* (e.g., the central nervous system, kidneys, heart, and gastrointestinal tract).

a H U S

What is atypical hemolytic uremic syndrome (aHUS)?



aHUS is a **rare, life-threatening, complex, unpredictable disease** of ***uncontrolled complement activation that manifests as complement-mediated TMA, which can lead to progressive, severe organ damage/failure***[1–5]

Associated with **dysregulation of the alternative pathway of complement** (pathologic variants and polymorphisms affecting the function of various complement proteins, **or CFH autoantibodies**)[4–8]

It can occur at any age, with a slightly **more frequent onset during childhood (nearly 60% vs 40% during adulthood)**[6]

The disease has a **poor prognosis with supportive care**[5,7,9]

1. *Jamme M et al. PLoS One. 2017;12(5):e0177894;* ***2.*** *Cofiell R et al. Blood. 2015;125(21):3253-62;* ***3.*** *Goodship TH et al. Kidney Int. 2017 Mar;91(3):539-51;* ***4.*** *Nester CM et al. ASH Education Program Book. 2012 December 8, 2012;2012(1):617-25;* ***5.*** *Fremeaux-Bacchi V et al. Clinical Journal of the American Society of Nephrology. 2013;8(4):554-62;* ***6.*** *Loirat C et al. Orphanet Journal of Rare Diseases. 2011 September 08;6(1):60;* ***7.*** *Noris M et al. Clinical Journal of the American Society of Nephrology. 2010;5(10):1844-59;* ***8.*** *Bresin E et al. J Am Soc Nephrol. 2013 Feb;24(3):475-86;* ***9.*** *Schaefer F et al. Kidney International. 2018;94(2):408-18.*

AP, alternative pathway; CFH, complement factor H; TMA, thrombotic microangiopathy.

INCIDENZA ANNUA

circa 2 casi per milione di persone nel soggetto adulto
Circa 3,3 casi per milione di persone in età pediatrica.

Può manifestarsi a qualsiasi età, ma l'esordio durante l'infanzia è più frequente rispetto all'età adulta

rappresenta circa il 10% dei casi di SEU nei bambini, la maggior parte dei casi di SEU negli adulti.

Può essere sporadica o familiare. Tra i pazienti affetti da SEUa con mutazioni genetiche, circa il 67% si manifesta durante l'età pediatrica.

aHUS incidence and prevalence

All individuals[2,a]
Prevalence: **4.9/million people**
Annual incidence: **0.23–1.9/million people**

Patients aged ≤20 years[2,a]
Prevalence: **2.2–9.4/million people**
Annual incidence: **0.26–0.75/million people**

~2 cases/million people/year in the US[3,4]

~0.11 to 0.23 cases/million people in Europe[1,5]

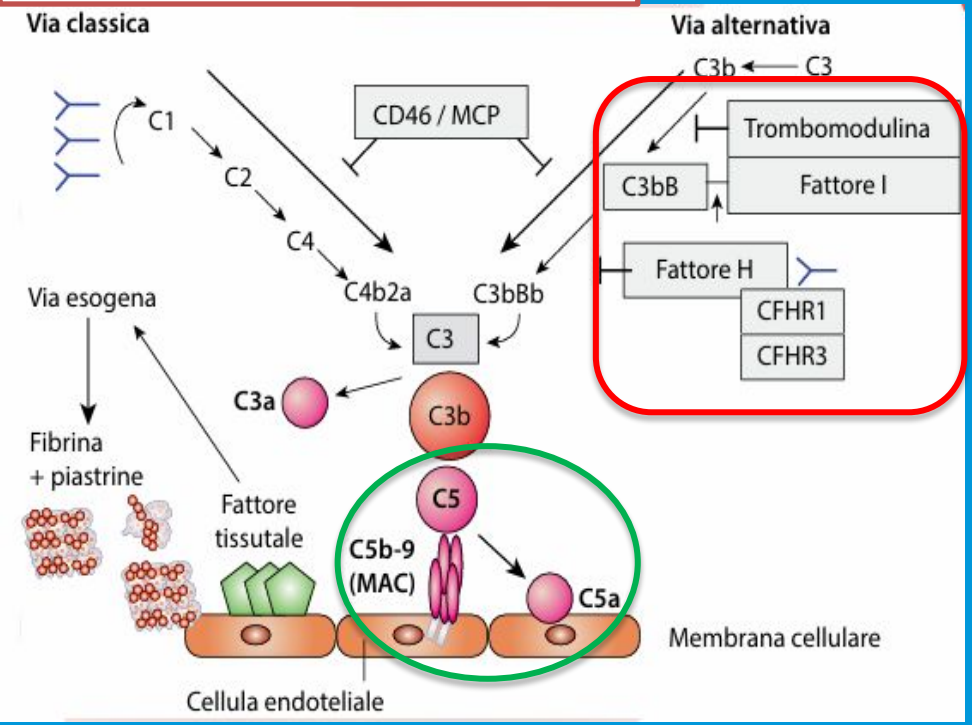
~0.79 to 1.58 diagnosed cases/million people in Japan[3,b]

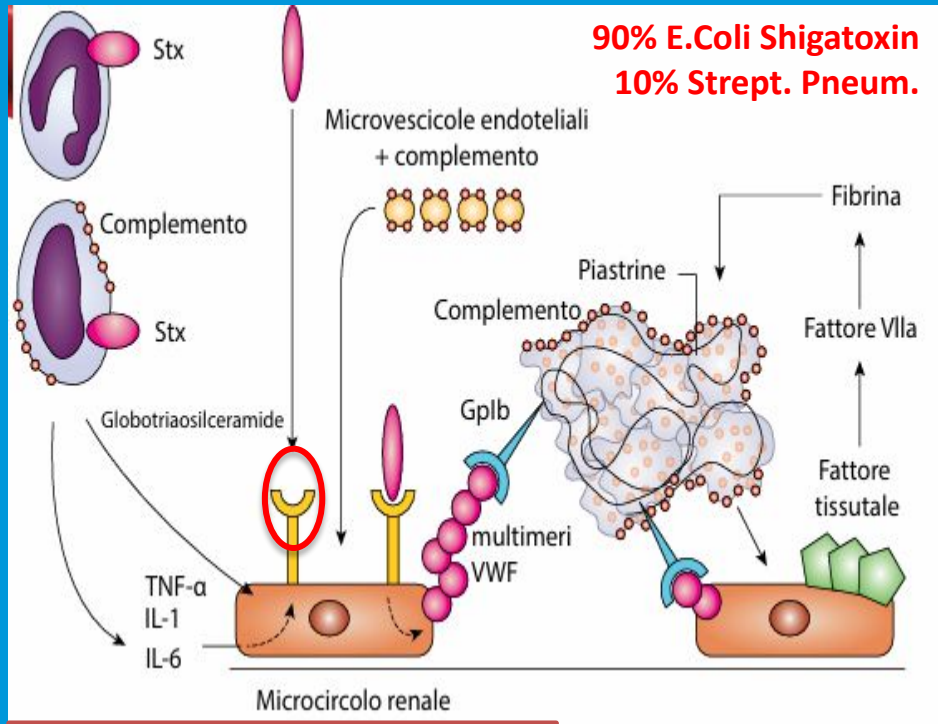
About 50% (387/851) of patients are diagnosed before the age of 18 years[6,c]

23% (49/217) of patients saw 4 or more physicians prior to their diagnosis[7,d]

[a]*Based on a systematic literature review of studies in Europe and Oceania.* [b]*Based on a cohort study done in 2017, which estimated that 100–200 patients in Japan had been diagnosed with aHUS, and the Japan population in 2017 (126.8 million as reported by World Bank in 2017).*[3] [c]*From a study of 851 adult and pediatric patients in the global aHUS registry.*[5]
[d]*From a poll of 214 participants from 17 countries who took part in the RareConnect International Survey in 2014.*[6]
1. *Campistol JM et al. Nefrologia 2015;35:421–47.* **2.** *Yan K et al. Clin Epidemiol 2020;12:295–305.* **3.** *Yoshida Y et al. Ren Replace Ther 2017;3:5.* **4.** *Constantinescu AR et al. Am J Kidney Dis 2004;43:976–82.* **5.** *Fremeaux-Bacchi V et al. Clin J Am Soc Nephrol 2013;8:554–62.* **6.** *Schaefer F et al. Kidney Int 2018;94:408–18.* **7.** *Results of RareConnect International aHUS Survey. http://www.ahuscanada.org/results-of-rareconnect-international-ahus-survey. Accessed November 2021.*
aHUS, atypical hemolytic uremic syndrome.

SEU ATIPICA IMMUNOLOGICA



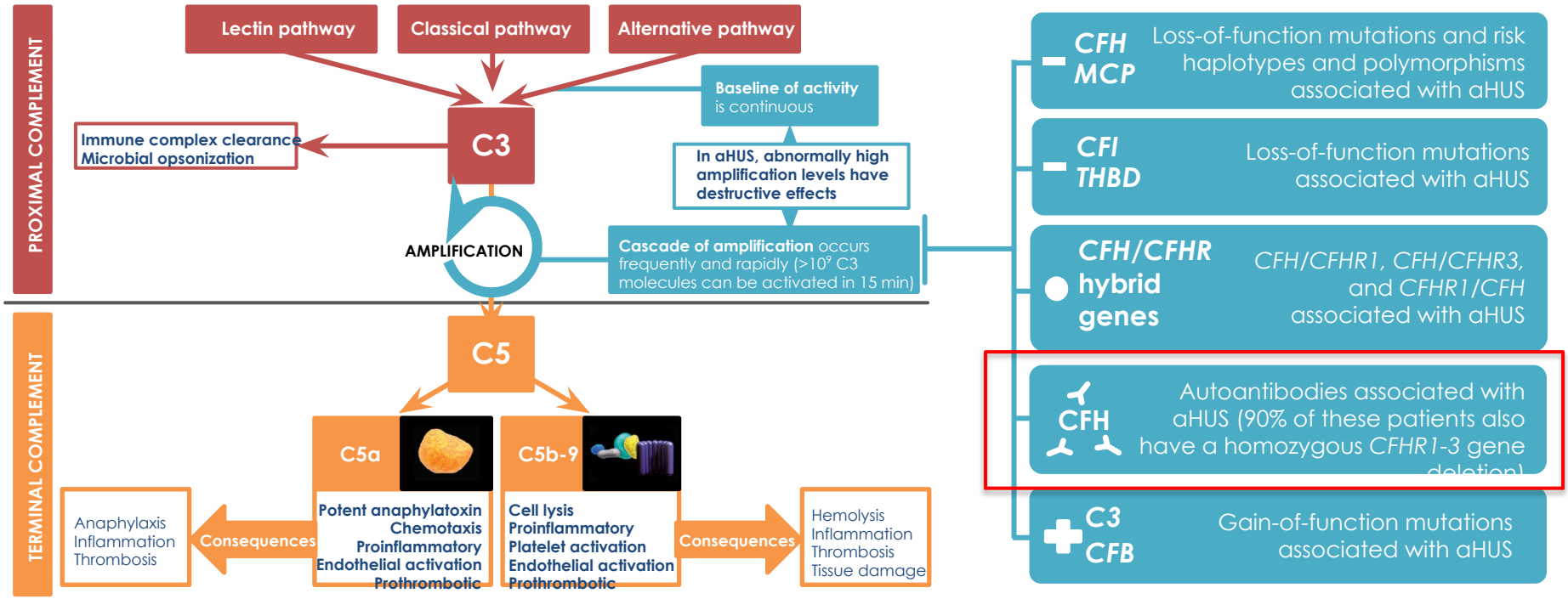


90% E.Coli Shigatoxin
10% Strept. Pneum.

SEU CLASSICA INFETTIVA

Recettore su endotelio particolarmente dei capillari glomerulari di neonati e bambini

Genetic mutations, polymorphisms, autoantibodies and uncontrolled complement activity[1–6]



1. *Noris M et al. Nat Rev Nephrol 2012;8:622–33.* **2.** *Campistol JM et al. Nefrologia 2015;35:421–47.* **3.** *Jokiranta TS. Blood 2017;129:2847–56.* **4.** *Maga TK et al. Hum Mutat 2010;31:E1445–60.* **5.** *Noris M et al. Clin J Am Soc Nephrol 2010;5:1844–59.* **6.** *Noris M, Remuzzi G. N Engl J Med 2009;361:1676–87.*
aHUS, atypical hemolytic uremic syndrome; C3, complement component 3 gene; CFB, complement factor B gene; CFH, complement factor H gene; CFHR1, complement factor H-related protein 1; CFI, complement factor I gene; MCP, membrane cofactor protein gene; THBD, thrombomodulin gene.

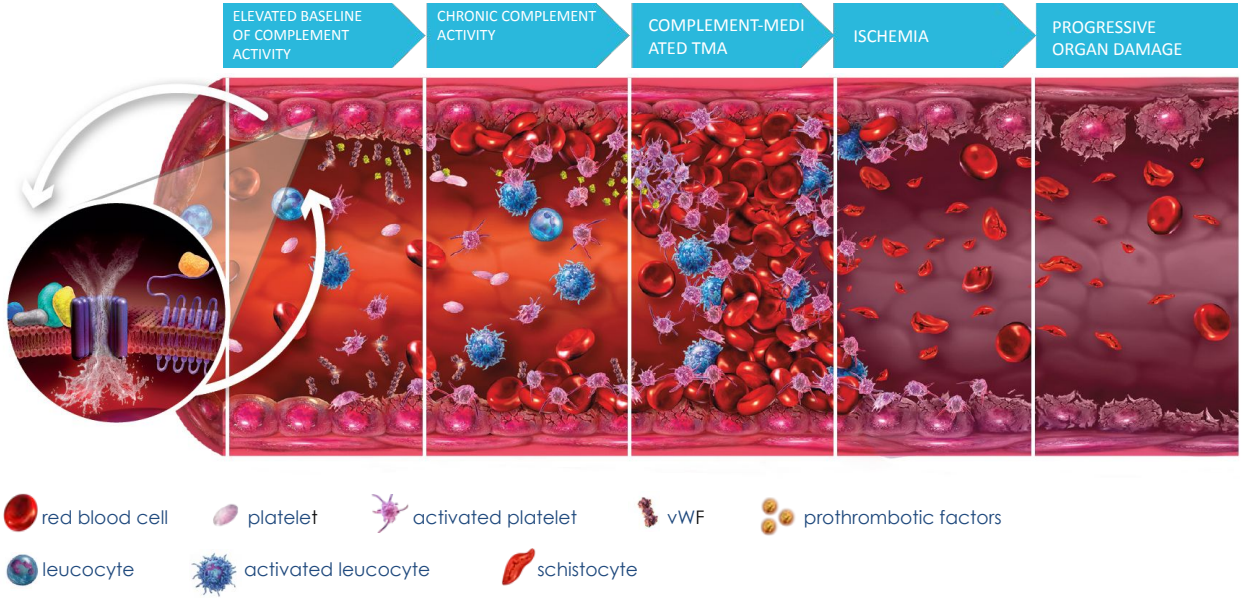
Tabella 5.1. Fattori genetici della via alternativa del complemento coinvolti nella patogenesi della sindrome emolitico-uremica complemento-mediata (CM-HUS).

Mutazione	Frequenza	Tipo	Rischio morte e/o IRT (pre-Ecu)	Rischio recidiva (post-Ecu)*	Età di esordio (picco)
CFH	30%	Eterozigosi › regione SCR 19-20	70-80%	64%	0-4 anni
MCP	15%	Eterozigosi	‹20%	37%	1-12 anni
CFHR1-CFHR3:	6-10%	Delezione, presente in ›90% DEAP-HUS (Ab anti-CFH)	30-40%	20%	3-8 anni
CFHR1 e CFHR3	3-5%	Gene ibrido CFH/CFHR1	-	-	-
CFI	8-10%	Eterozigosi	60-70%	23%	0-4 anni
C3	5-10%	Attivanti o "gain of function"	60-70%	14%	1-10 anni
CFB	1-4%	Attivanti o "gain of function"	-	-	-
Mutazioni combinate	1-3%		-	-	0-2 anni
Nessuna mutazione identificata	30-35%		50%	3,5%	Tutta l'età pediatrica

**Noris CJASN 2010, Fakhouri Blood 2021.*
IRT: insufficienza renale terminale; FCH: fattore H, CFI: fattore I, CFB: fattore B, Ecu: eculizumab.

TMA lesions and tissue damage[1]

Vicious cycle of complement amplification and endothelial injury[2]



Chronic, uncontrolled complement activity and endothelial damage put patients with aHUS at risk of life-threatening complications[2–4]

1. *Goodship THJ et al. Kidney Int 2017;91:539–51.* ***2.*** *Noris M et al. Nat Rev Nephrol 2012;8:622–33.* ***3.*** *Le Quintrec M et al. Am J Transplant 2013;13:663–75.*
4. *Macia M et al. Clin Kidney J 2017;10:310–19.*
aHUS, atypical hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

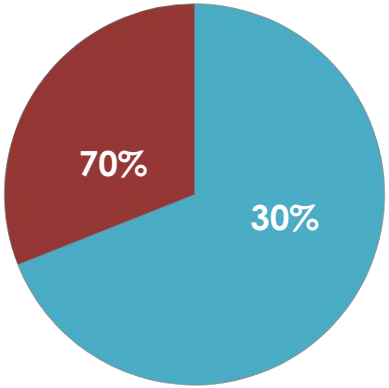
Non-genetic causes of aHUS

- **In some cases, genetic mutations alone are not enough to cause aHUS[1]**
- **aHUS is often unmasked by a new or preexisting condition that promotes complement activation and endothelial damage (trigger)[1,2]**

aHUS unmasked by a trigger[2,a]

Triggers

- Pregnancy
- Malignant hypertension (MHT)
- Transplant (organ/bone marrow)
- Certain medications
- Infection
- Autoimmune diseases
- Surgery/trauma
- Other



70% (191/273) of patients with aHUS presented their first clinical manifestations while experiencing a trigger[2,a]

aHUS with no identifiable trigger [2,a]

Nei pazienti con aHUS però il trattamento del trigger non risulta sufficiente a fermare la cascata innescata

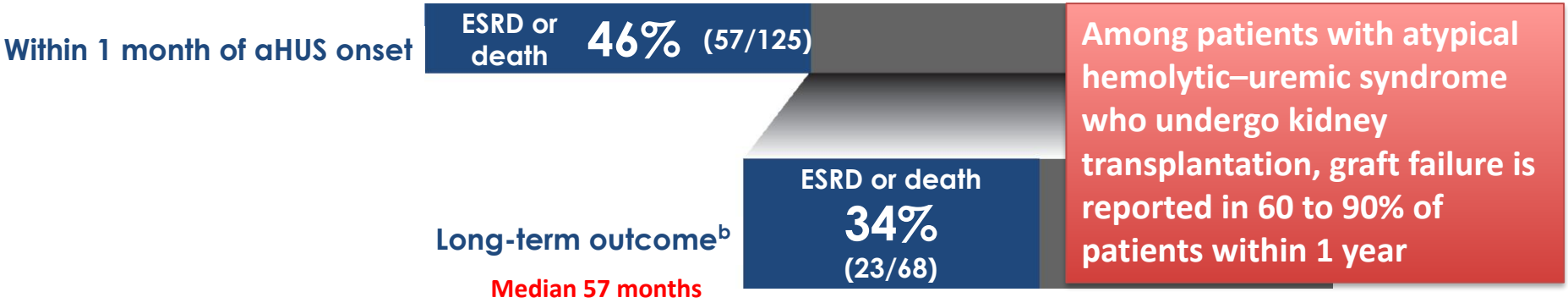
[a]*From a study of 273 patients with aHUS enrolled in the International Registry of Recurrent and Familial HUS/TTP between 1996 and 2007.*[2]

1. *Riedl M et al. Semin Thromb Hemost 2014;40:444–64.* **2.** *Noris M et al. Clin J Am Soc Nephrol 2010;5:1844–59.*

aHUS, atypical hemolytic uremic syndrome.

Outcomes of TMA in patients with aHUS

Over one third of adult patients with aHUS who survived a first TMA manifestation without ESRD progressed to ESRD or death within 5 years[1,a]



Among pediatric patients, 17% (15/89) progressed to ESRD or death within 1 month following first TMA manifestation and 36% (32/89) progressed to ESRD or death within 5 years[1,c]

[a]Retrospective analysis of 125 adult (≥16 years) and 89 pediatric French patients with aHUS assessed the effect of complement gene mutations on disease onset, presentation, and outcome.[3] [b]Additional patients experiencing ESRD or death at last follow-up: median follow-up of 57 months (range, 1-353 months).[3] [c]Median follow-up of 45 months (range, 1-493 months).[3]

1. *Fremeaux-Bacchi V et al. Clin J Am Soc Nephrol 2013;8:554–62.*

aHUS, atypical hemolytic uremic syndrome; ESRD, end-stage renal disease; TMA, thrombotic microangiopathy.

DIAGNOSI aHUS (SEUa)

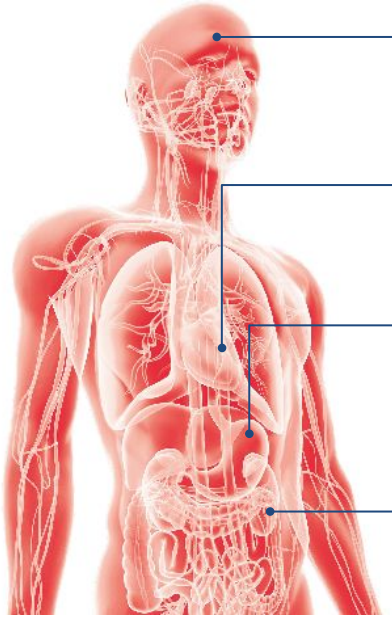
PIASTRINOPENIA MODERATA-SEVERA

ANEMIA EMOLITICA NON AUTOIMMUNE

DANNO D'ORGANO SPECIE RENALE

ESCLUSIONE PTT E SEU TIPICA

Patients with aHUS and risk of complications[a,9]



Up to 48% **experience neurological symptoms, including[5]:**

- Confusion[3]
- Encephalopathy[4,5]
- Stroke[5]
- Seizure/epilepsy[3]

Up to 43% **experience CV symptoms, including[8]:**

- Arterial thrombosis[5]
- Vascular stenosis[4]
- Cardiomyopathy[3]
- Hypertension (often malignant)[3]
- Myocardial infarction[4,5]

Up to 37% **experience GI symptoms, including[5]:**

- Colitis[5]
- Abdominal pain[3]
- Pancreatitis[5]
- Nausea/vomiting[5]
- Gastroenteritis[2,7]
- Diarrea anche sanguinolenta[3]

More than 50% **progress to ESRD[4,5]:**

- Elevated creatinine[3]
- Decreased eGFR[1]
- Proteinuria oligoanuria ematuria, edemi declivi[6]

Other macrovascular complications[8]:

- **Peripheral arterial disease**
- **Phalangeal gangrene**

[a]*The organ-specific symptoms associated with aHUS are reported from the published literature and are not limited to only those listed in this slide.*

1. *Legendre CM et al. N Engl J Med 2013;368:2169–81.* ***2.*** *Goodship THJ et al. Kidney Int 2017;91:539–51.* ***3.*** *Jamme M et al. PLoS One 2017;12:e0177894.* ***4.*** *Hofer J et al. Front Pediatr 2014;2:97.* ***5.*** *Campistol JM et al. Nefrologia 2015;35:421–47.* ***6.*** *Krishnappa V et al. Ther Apher Dial 2018;22:178–88.* ***7.*** *Schonermarck U, Ries W et al. Clin Kidney J 2020;13:208-16.* ***8.*** *Noris M, Remuzzi G. Nat Rev Nephrol 2014;10:174–80.* ***9.*** *Yerigeri K et al. J Multidiscip Healthc 2023;16:2233-2249.*

aHUS, atypical hemolytic uremic syndrome; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GI, gastrointestinal.

1 DANNO D'ORGANO

Sintomi gastrointestinali
Dolore addominale e/o nausea/vomito e/o diarrea e/o diarrea sanguinolenta e/o gatroenterite/pancreatite

Sintomi neurologici
Ictus e/o confusione e/o crisi epilettiche e/o convulsioni e/o coma

Sepsi
Febbre e/o infezioni

Sintomi cardiovascolari
Infarto miocardio e/o ictus e/o ipertensione e/o stenosi arteriosa e/o gangrena periferica

Compressione renale
Osgo-anuria, edemi, aumento della creatina, proteinuria, micro/macroematuria

Sintomi polmonari
Dispmea e/o emorragia polmonare e/o edema polmonare

Altri
Affaticamento/astenia e/o porpora/petecchie

Sintomi Oculari
Dolore e offuscamento visivo e/o occlusione dei vasi retinici e/o emorragia oculare

+

Piastrinopenia
‹ 70000 (<25% della nota)

+

Anemia Hg‹10
LDH ≥330

Se presente solo una, ripetere a 24 e 48h

RICOVERO IN TI/TSI Multidisciplinare MEU

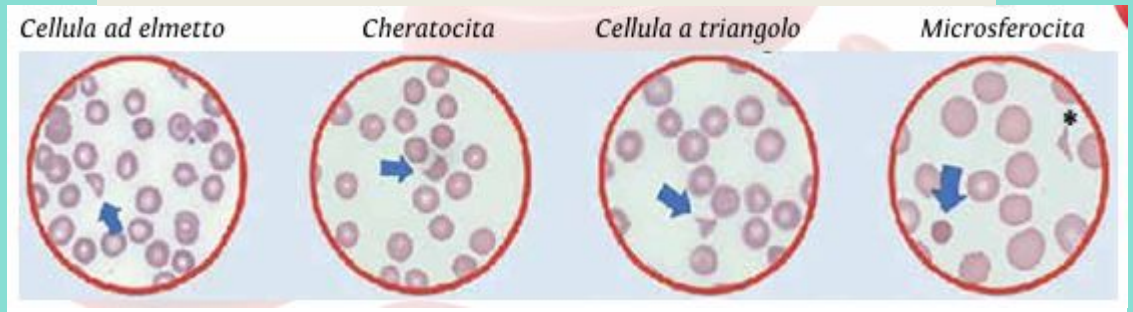
Anemia + Piastrinopenia + LDH aumentato

APTOGLOBINA ↓
RETICOLOCITI ↑
SCHISTOCITI >2%
BILIRUBINA ↑ indir
COOMBS Negativo
PTT INR D-D Normali

Studio del complemento inutile

XIII congresso nazionale
simeu
GENOVA 30 MAG - 1 GIU 2024

SCHISTOCITI



la mancanza di schistociti non esclude a priori la diagnosi di TMA

IL TEST DI COOMBS E' POSITIVO NELLA SEU DA PNEUMOCOCCO

EGA = acidosi metabolica con lattati alti

Danno renale se

1. aumento di 1,5 volte della creatininemia nota
2. di 0,3 mg/dl in 48h;
3. Proteinuria e albuminuria nel 50%

Danno d'organo con
Amilasi, Lipasi
Troponina BNP
AST/ALT/FA/GGT

Sospetta TMA
Anemia, piastrinopenia, aumento creatinina e LDH, aptoglobina bassa, schistociti, danno renale
Escludere Anemia emolitica autoimmune: test di Coombs negativo, escludere CID, escludere infezioni (virus, S Pneumoniae)

Porpora trombotica trombocitopenica (PTT)?
Attività ADAMTS13 <10%

< 72h

SEU tipica (STEC-HUS)?
VTEC in colture feci, sierologia e/o PCR positiva

Attività ADAMTS13 >10% e VTEC negativo: SEU atipica (a-HUS)

Forme secondarie?
farmaci, gravidanza, ipertensione, neoplasie, trapianto organo solido, trapianto midollo, malattie autoimmuni

Deficit Cianocobalamina C?
Dosaggio omicisteina plasmatica, acidi organici urinari, vitamina B1, genetica per MMACHC

Escluse forme secondarie e deficit cianocobalamina C: SEU complemento-mediate (CM-HUS)
Screening genetico e sierologico via alternativa del complemento

Tabella 6.1. Farmaci che hanno riportato una probabile o definita associazione con la TMA.

Farmaci chemioterapici	Terapie a bersaglio molecolare	Farmaci immunosoppressori	Antibiotici e antivirali	Altri farmaci/sostanze tossiche
Farmaci che presentano un'associazione definita con la TMA				
Bortezomib	Alemtuzumab	Ciclosporina A	Levofloxacina	Onasemnogene abeparvovec
Docetaxel	Moxetumomab pasudotox	Tacrolimus	Sulfisossazolo	Acido valproico
Gemcitabina	Imatinib mesilato	Interferon (alfa, beta, policarbossilato)		Ossicodone cloridrato
Oxaliplatino	Lenvatinib	Leflunomide		Ossimorfone
Mitomicina C	Nintedanib	Sirolimus		Quetiapina
Vincristina	Palbociclib	Everolimus		Chinino
Doxorubicina Liposomiale Pegilata	Regorafenib	Certolizumab pegol		Cocaina
Pentostatina	Sunitinib			Trielina
Carfilzomib	Bevacizumab			
Ixazomib	Ramucirumab			
Farmaci che presentano un'associazione probabile con la TMA				
Lomustina	Pazopanib	Adalimumab	Ciprofloxacina	Clopidogrel
Tamoxifene		Muromonab-CD3	Metronidazolo	Simvastatina
Trastuzumab			Penicilline	Idrossiclorochina
Daunorubicina			Rifampicina	Estrogeni/Progesterone
			Trimetoprim-Sulfametoxazolo	Bupropione
			Famciclovir	Ecstasy
			Valacyclovir	

ANA - Antifosfolipidi
Omocisteina
B12

EXCLUDE OTHER CAUSES OF TMA

DIC: prothromb in time and aPTT prolonged; fibrinogen low (or low-normal with infection); D-dimers high; antithrombin and protein C low
Evans syndrome, S. pneumoniae HUS, Autoimmune hemolytic anemia: 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 hematopoietic 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

ADAMTS13 activity < 10%	ADAMTS13 activity > 10%	Shiga-toxin/EHEC positivity
TTP	aHUS	STEC-HUS

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

PROBLEMI

POCT ADAMTS13

1. **Solo ISS esegue AB anti-LPS dei sierogruppi STEC**
2. **Feci e/o tampone rettale prima di terapia antibiotica per ricerca geni stx codificanti Shiga Toxins e isolamento ceppo**

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Test	Outcome in aHUS	Alternative Diagnosis
Reticulocyte counts	Increased	
Free serum hemoglobin	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
Hemoglobin	Decreased	Can be decreased in all TMAs
Serum creatinine	Increased (most of the time)	Can be increased in all TMAs
Hematuria and proteinuria	Present (most of the time)	Can be present in all TMAs
Kidney biopsy[a]	Often arteriolar and/or glomerular intracapillary thrombosis if kidney affected	
Direct antiglobulin test (Coombs test)	Negative	Positive in autoimmune hemolytic anemias, 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 postpartum	Pregnancy-triggered TMA caused by TTP usually presents during pregnancy
Antibody testing, including antinuclear antibody, lupus anticoagulant, and antiphospholipid antibodies	Negative	Positive in systemic diseases, such as SLE, CAPS; 30% of TTP have positive antinuclear antibodies
Rule out TTP and STEC-HUS		
STEC infection: fecal sample or rectal swab test for *Escherichia 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

Tabella 3.IV. PLASMIC SCORE e FRENCH score.

Parametri	Punti per PLASMIC score	Punti per French score
Creatinina ‹2,0 mg/dl o ‹177 mol/l ‹2,273 mg/dl o ‹200 mol/l	1	 1
Conta piastrinica ‹30000/mm^3	1	1
Parametri di emolisi • Conta reticolocitaria ›2,5% • Bilirubina indiretta 2,0 mg/dl • Aptoglobina soppressa	1	
No neoplasie attive	1	
No storia di trapianto di organo solido o midollo	1	
MCV ‹90 fl	1	
INR ‹1,5	1	
Correlazione score-predittività	0-4 = 0-4% 5 = 5-24% 6-7= 62-82%	0=2% 1=70% 2=94%

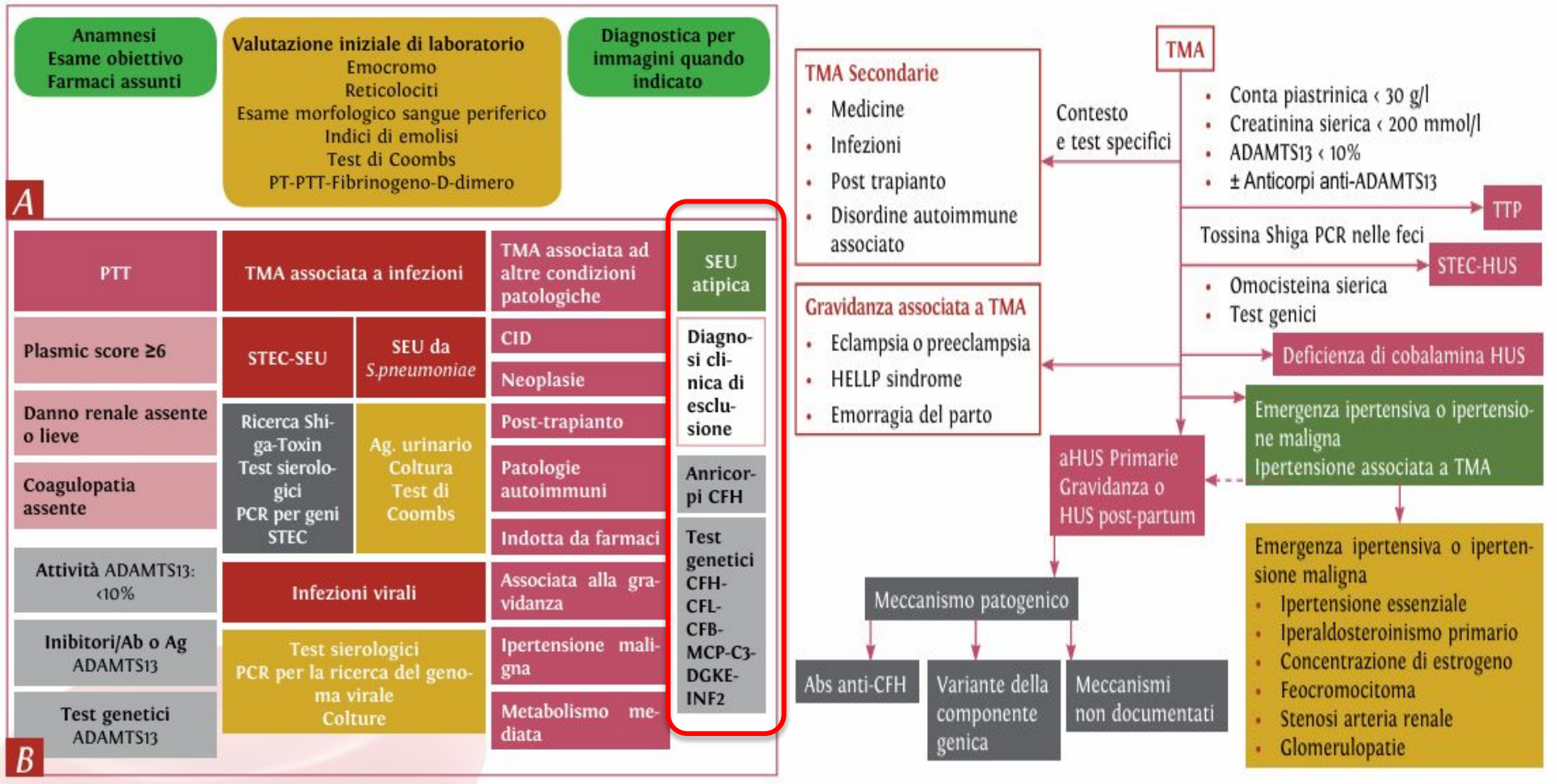
Plasmic/French score e SEUa

in un contesto di danno d'organo e di anemia emolitica Coombs negativa

Se Plasmic Score < 5,
specie per
piastrine >30000/mmc e
creatinina > 2 mg/dl,

quindi soprattutto se French Score = 0

si deve sospettare clinicamente una forma SEU


Anamnesi
Esame obiettivo
Farmaci assunti
Valutazione iniziale di laboratorio
Emocromo
Reticolociti
Esame morfologico sangue periferico
Indici di emolisi
Test di Coombs
PT-PTT-Fibrinogeno-D-dimero
Diagnostica per immagini quando indicato
A
PTT
Plasmic score ≥6
Danno renale assente o lieve
Coagulopatia assente
Attività ADAMTS13: <10%
Inibitori/Ab o Ag ADAMTS13
Test genetici ADAMTS13
B
TMA associata a infezioni
STEC-SEU
SEU da S.pneumoniae
Ricerca Shiga-Toxin
Test sierologici
PCR per geni STEC
Ag. urinario
Coltura
Test di Coombs
Infezioni virali
Test sierologici
PCR per la ricerca del genoma virale
Colture
TMA associata ad altre condizioni patologiche
CID
Neoplasie
Post-trapianto
Patologie autoimmuni
Indotta da farmaci
Associata alla gravidanza
Ipertensione maligna
Metabolismo mediata
SEU atipica
Diagnosi clinica di esclusione
Anricorpi CFH
Test genetici CFH-CFL-CFB-MCP-C3-DGKE-INF2
TMA
Conta piastrinica ‹ 30 g/l
Creatinina sierica ‹ 200 mmol/l
ADAMTS13 ‹ 10%
± Anticorpi anti-ADAMTS13
TTP
Tossina Shiga PCR nelle feci
STEC-HUS
Omocisteina sierica
Test genici
Deficienza di cobalamina HUS
Contesto e test specifici
TMA Secondarie
Medicine
Infezioni
Post trapianto
Disordine autoimmune associato
Gravidanza associata a TMA
Eclampsia o preeclampsia
HELLP sindrome
Emorragia del parto
aHUS Primarie
Gravidanza o HUS post-partum
Emergenza ipertensiva o ipertensione maligna
Ipertensione associata a TMA
Meccanismo patogenico
Abs anti-CFH
Variante della componente genica
Meccanismi non documentati
Emergenza ipertensiva o ipertensione maligna
Ipertensione essenziale
Iperaldosteroinismo primario
Concentrazione di estrogeno
Feocromocitoma
Stenosi arteria renale
Glomerulopatie

Thrombocytopenia in the ICU

- **Thrombocytopenia affects 25–55% of ICU patients**
- This combination of **thrombocytopenia** and **microangiopathic hemolytic anemia**, in which **thrombi** form in the microvasculature and **schistocytes** develop from red cell destruction as they pass over these thrombi, **occurs in patients with DIC, but also in those with TMAs**, including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)
- These clinical similarities of DIC, TTP, and HUS are a major concern because they pose a **risk of misdiagnosis** as intensivists are more likely to consider a diagnosis of DIC than of the rarer TTP or HUS, thus **delaying potentially lifesaving treatment**

Vincent JL et al. Critical Care 2018; 22:158; Azoulay E et al. Chest 2017;152:424–34; Ali N et al. J Community Hosp Intern Med Perspect. 2017;7:157–67.
DIC = disseminated intravascular coagulation; HUS = hemolytic uremic syndrome; ICU = intensive care unit; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

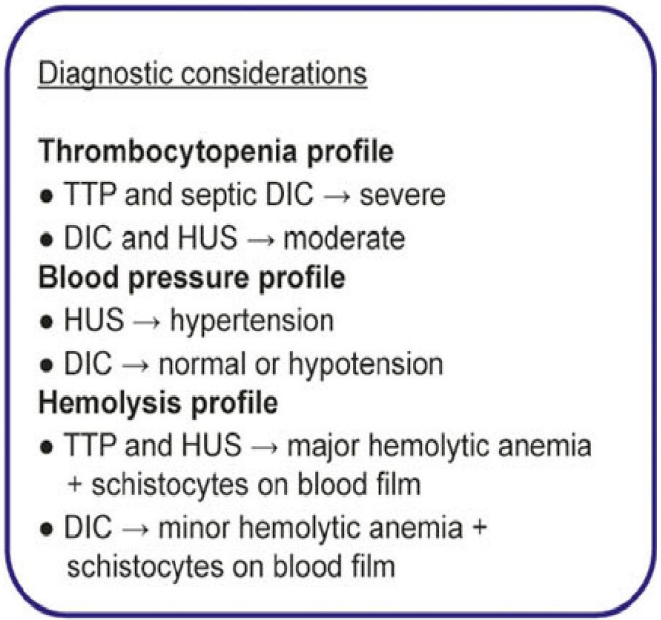
aHUS can be challenging to diagnose

- Similar to DIC, aHUS has a **rapid onset and non-specific presentation**
- aHUS can be found in association with other complement-activating states such as **infection, malignant hypertension, the post-partum period, kidney transplantation, certain drugs, or malignancies**
- There can be substantial **overlap in the presentation** of these conditions and they may coexist with complement-mediated aHUS, making distinction difficult
- **Rapid diagnosis and treatment** are essential to prevent irreversible organ damage and death

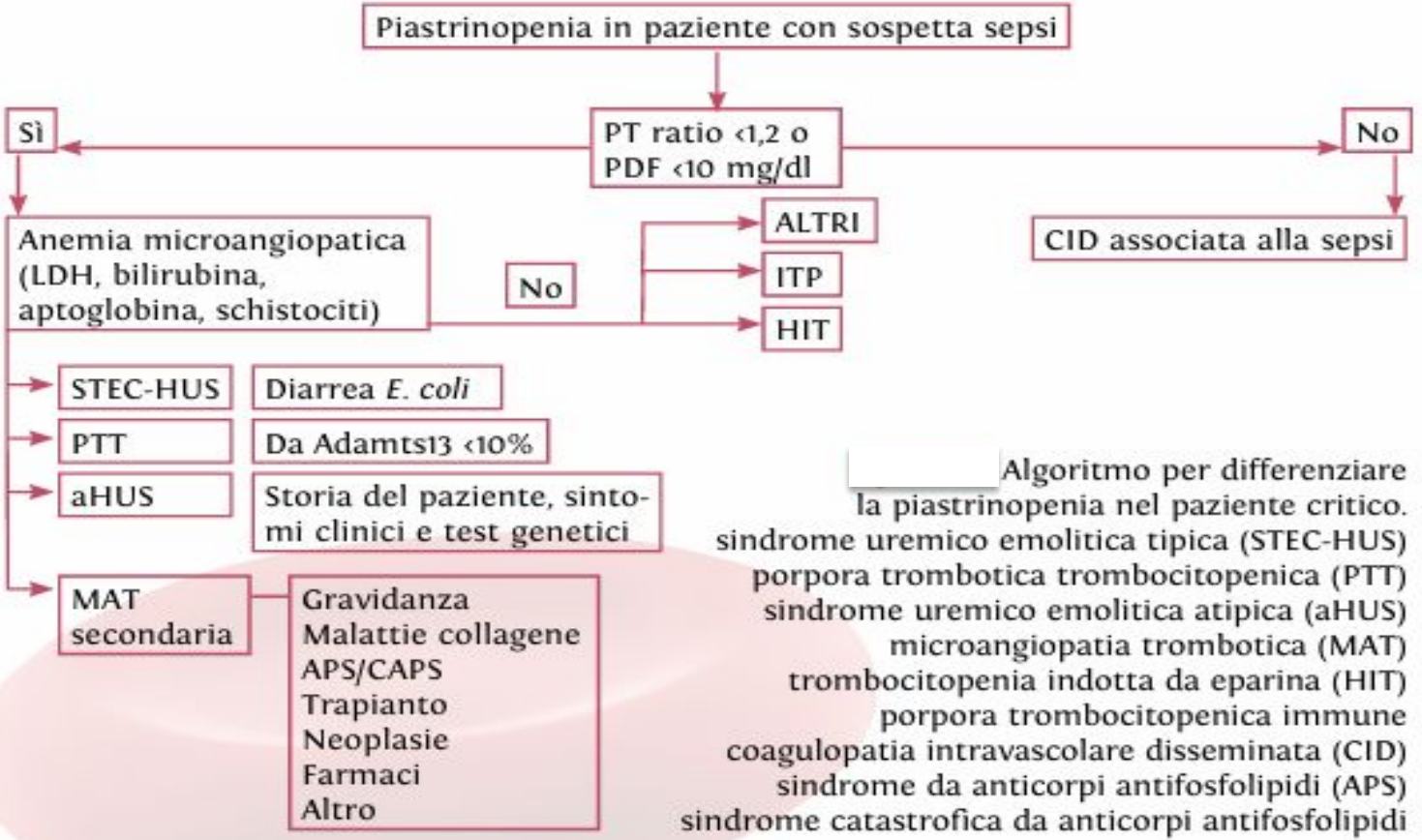
Vincent JL et al. Critical Care 2018; 22:158
aHUS = atypical hemolytic uremic syndrome; DIC = disseminated intravascular coagulation.

Differentiate DIC from TTP and HUS in the ICU

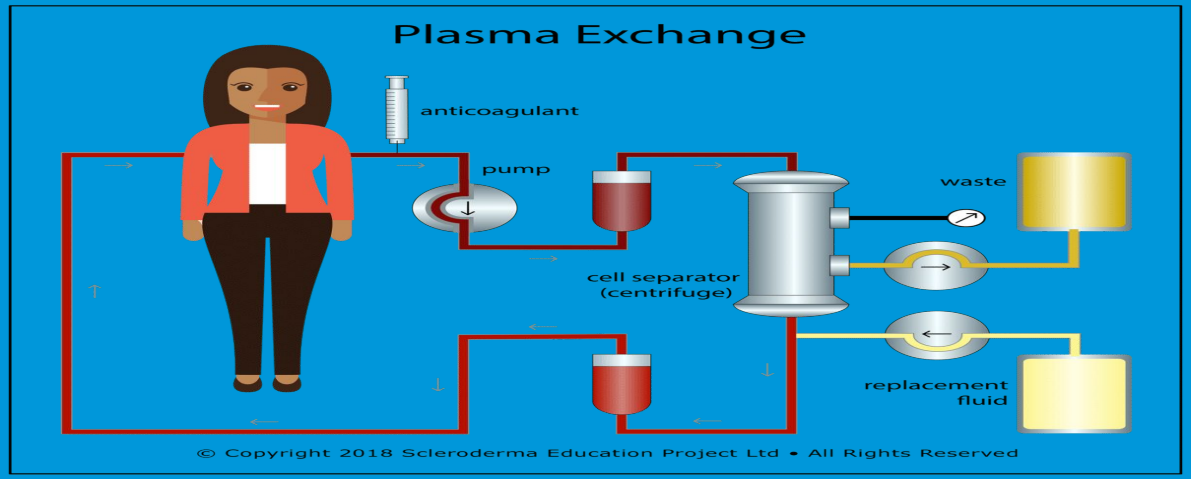
- **Microangiopathic hemolytic anemia**, negative Coombs test, **elevated LDH** levels, and organ dysfunction with **thrombocytopenia** are common to DIC, TTP, and aHUS, although patients with TTP and septic DIC may have more severe thrombocytopenia
- The most important distinguishing factor between DIC and TMAs is the **coagulation profile**, as patients with DIC have altered coagulation
- However, **blood pressure** is also important as HUS often presents with severe hypertension and DIC with hypotension



Vincent JL et al. Critical Care 2018; 22:158
aHUS = atypical hemolytic uremic syndrome; DIC = disseminated intravascular coagulation; HUS = hemolytic uremic syndrome; ICU = intensive care unit; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.



Algoritmo per differenziare la piastrinopenia nel paziente critico.
sindrome uremico emolitica tipica (STEC-HUS)
porpora trombotica trombocitopenica (PTT)
sindrome uremico emolitica atipica (aHUS)
microangiopatia trombotica (MAT)
trombocitopenia indotta da eparina (HIT)
porpora trombocitopenica immune
coagulopatia intravascolare disseminata (CID)
sindrome da anticorpi antifosfolipidi (APS)
sindrome catastrofica da anticorpi antifosfolipidi



TERAPIA

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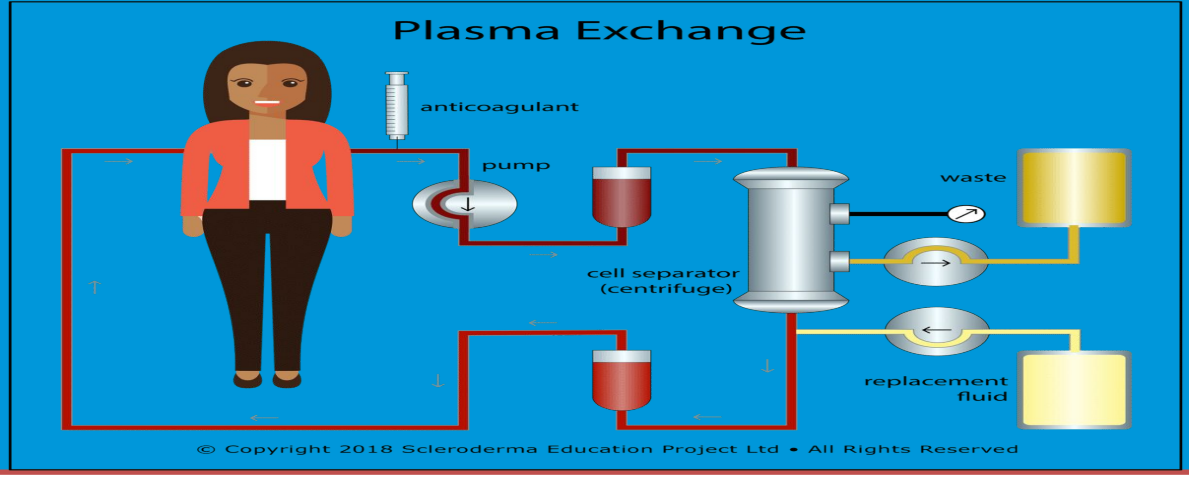
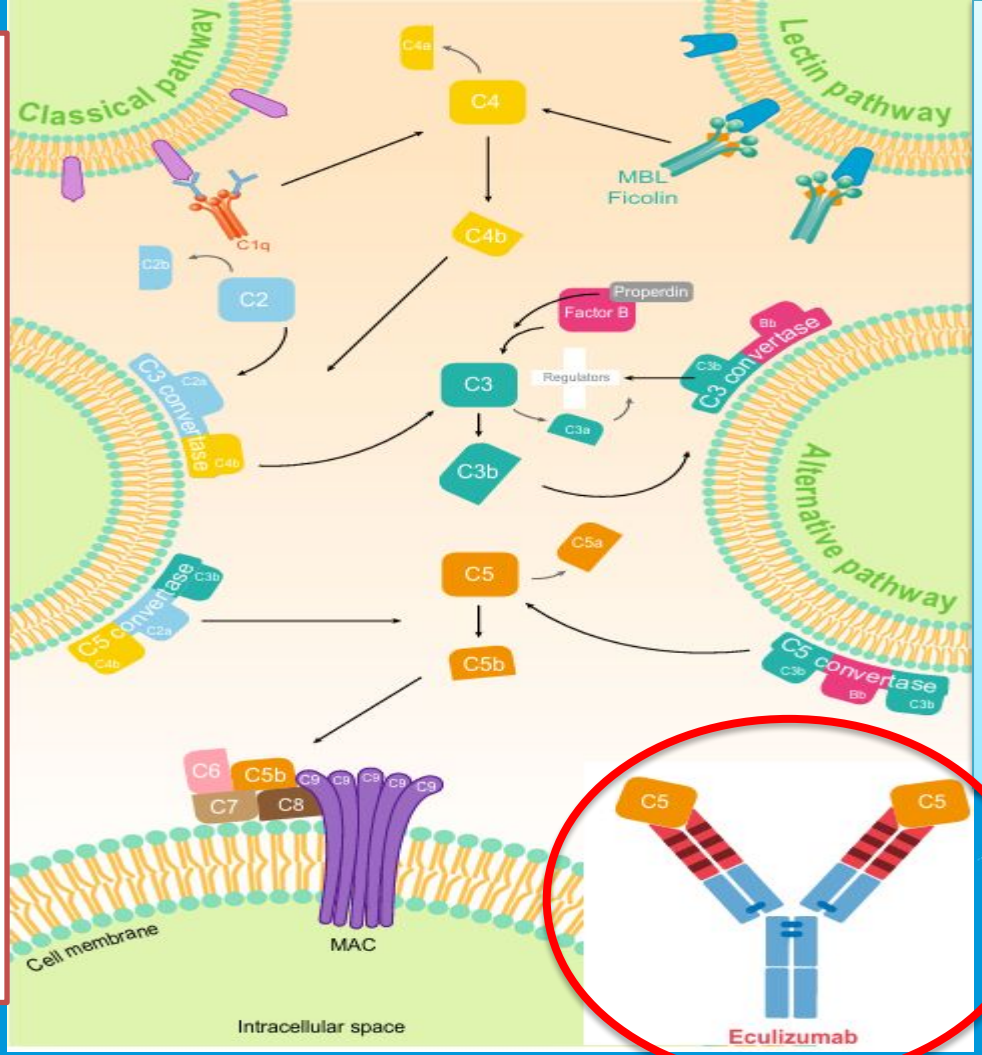


plasma fresco congelato (FFP), attraverso la plasmaferesi (plasma-exchange, PE) o le infusioni di plasma

i. **storicamente il trattamento di prima linea per la CM-HUS nell'era pre-eculizumab,**
ii. **permette di integrare i fattori regolatori del complemento carenti o disfunzionali.**
iii. **Fornisce proteine regolatrici del complemento**
iv. **ottiene anche la rimozione degli autoanticorpi (FHAA), delle proteine regolatrici del complemento disfunzionali e di altri potenziali fattori proinfiammatori o trombogenici coinvolti nel danno endoteliale.**
v. **Con questo approccio, la prognosi della CM-HUS era tipicamente sfavorevole, e la maggior parte dei pazienti sviluppava insufficienza renale terminale entro due anni dalla presentazione.**
vi. **Negli adulti, la plasmaferesi con plasma fresco congelato spesso viene iniziata in attesa delle indagini per escludere una PTT e le forme secondarie di SEU, mentre nei bambini non trova più indicazione, e può essere proseguita nelle forme con Ab anti-CFH**

After activation, C3 convertases (C2aC4a or C3bBb) are formed, and subsequently C5 convertases (C2aC4bC3b or C3bBbC3b), resulting in the formation of the lytic pore and end product of the complement system (C5b-C9).To prevent overactivation, the complement system is tightly controlled by various complement regula tors such as factor H and factor I.

Eculizumab is a humanized (chimeric) monoclonal antibody and is able to bind one or two C5 molecules, thereby preventing the cleavage of C5 into C5a and C5b, and hence blocking formation of C5b-C9. Fb factor b, MAC membrane attack complex, MBL mannose binding lectin



Atypical HUS results from an uncontrolled overactivation of AP due to pathogenic mutations of, or acquired auto antibodies directed against, complement regulatory proteins. This complement dysregulation causes endothelial activation and injury, resulting in platelet aggregation, formation of thrombi, and mechanical hemolysis

http://www.kidney-international.org clinical trial

OPEN

see commentary on page 882

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]

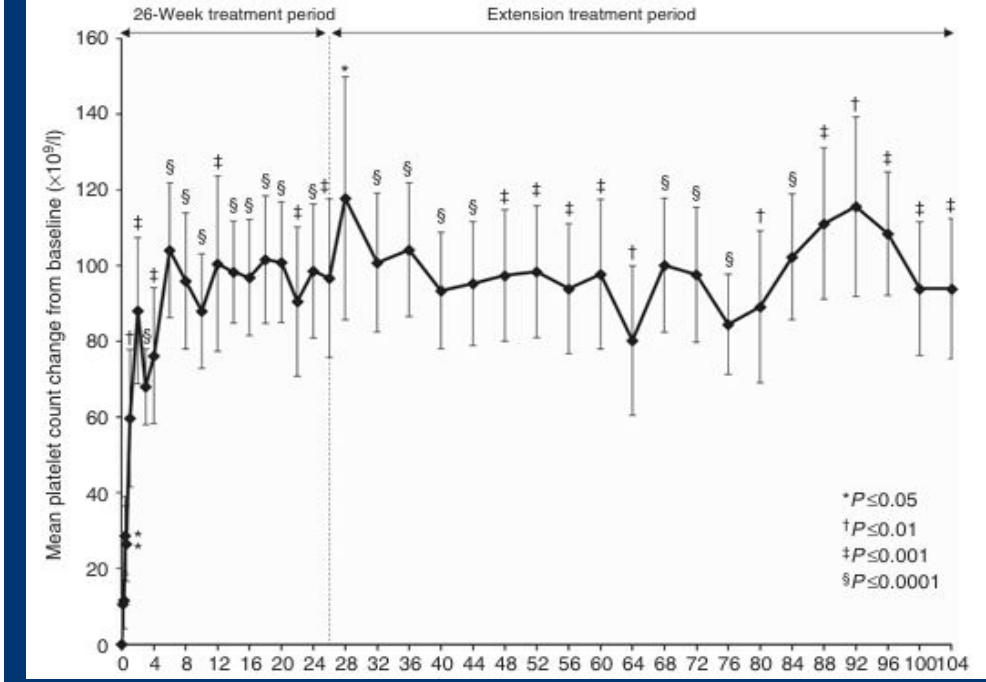
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 2013;368:2169-81.
DOI: 10.1056/NEJMoa1208981

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

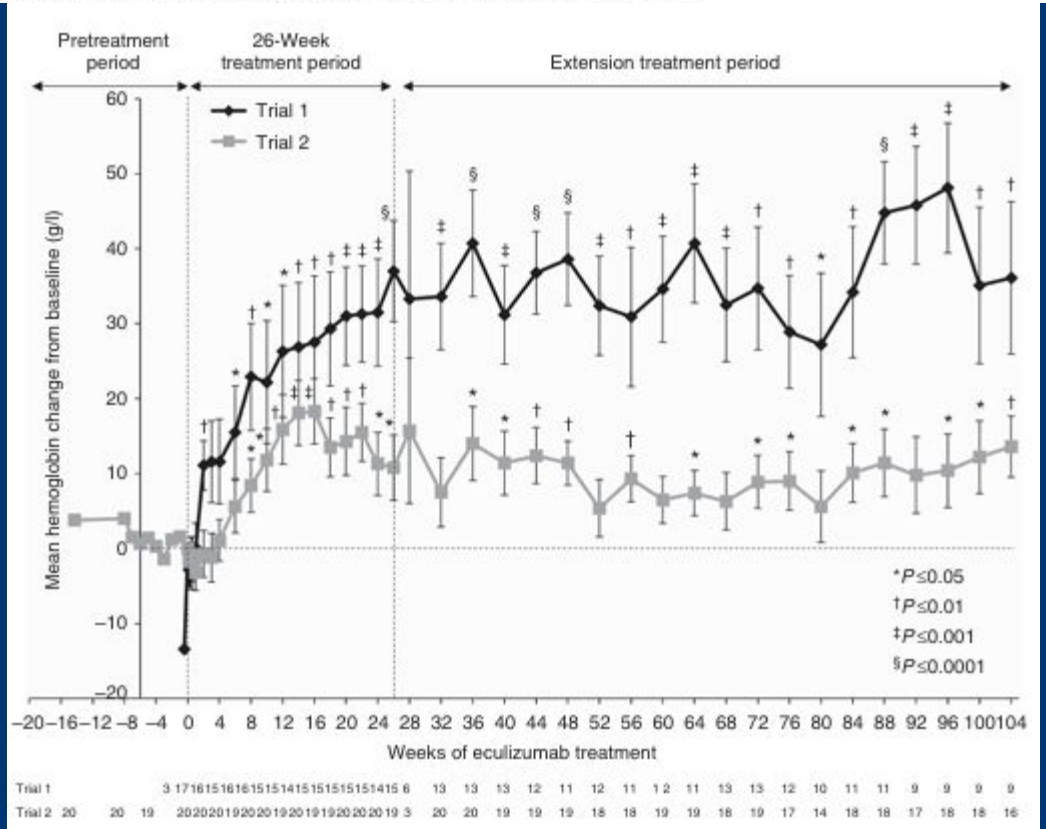


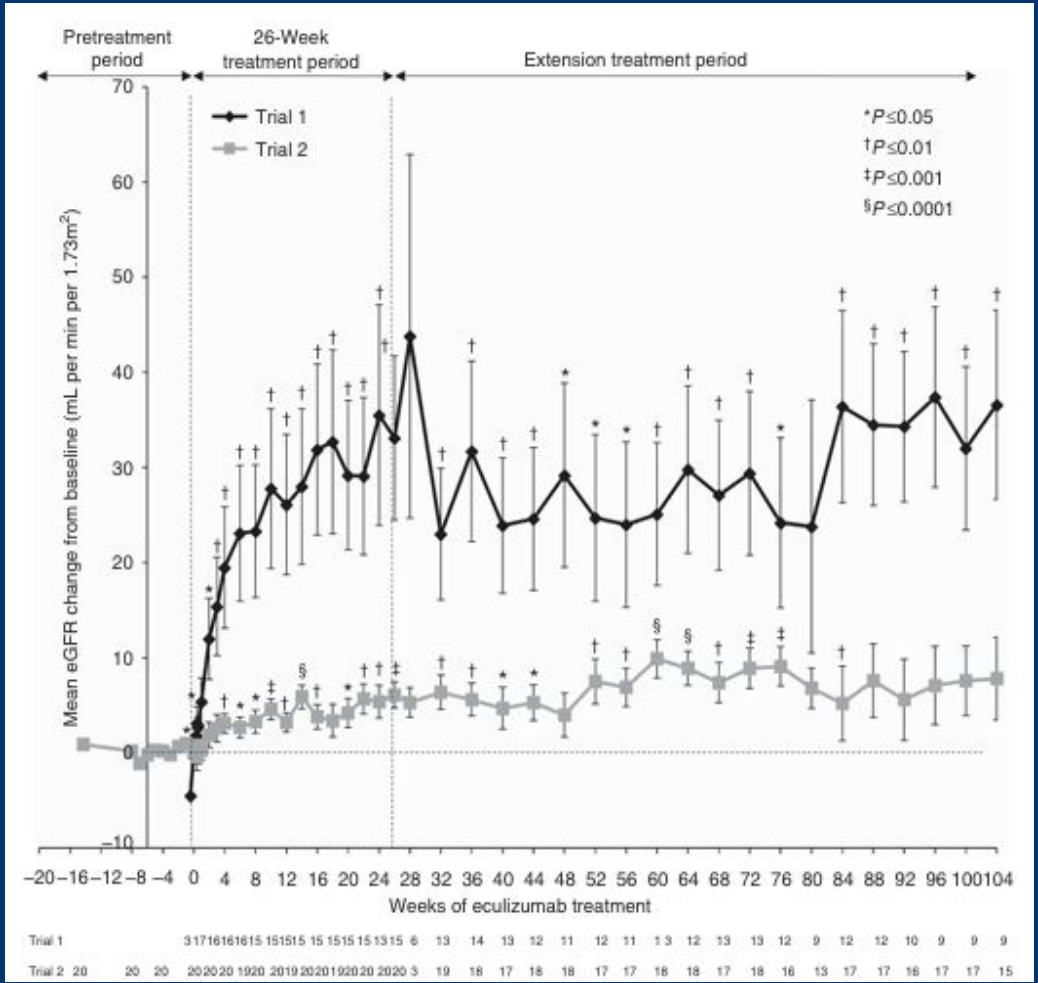
Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with atypical hemolytic–uremic syndrome.

Table 4 | Efficacy outcomes at the 2-year cutoff in patients with and without identified complement abnormalities[a]

Outcome, *n* (%)	Trial 1 ($N = 17$)		Trial 2 ($N = 20$)	
	Patients with identified abnormalities ($n = 13$)	Patients with no identified abnormalities ($n = 4$)	Patients with identified abnormalities ($n = 14$)	Patients with no identified abnormalities ($n = 6$)
TMA event-free status	12 (92)	3 (75)	14 (100)	5 (83)
Complete TMA response	11 (85)	2 (50)	7 (50)	4 (67)

Abbreviation: TMA, thrombotic microangiopathy.
[a]Includes complement gene mutations and polymorphisms and complement factor H autoantibodies.





Only patients in trial 1, who were treated earlier than patients in trial 2, showed ongoing, significant improvement in eGFR between years 1 and 2

Early treatment initiation may offer patients the best possible chance to recover renal function. The mechanism by which eculizumab leads to gains in renal function is not known, but it may involve kidney remodeling, ongoing dissolution of thrombi,maintenance of controlled blood pressure, and/or normalization of endothelial cell structure and function.

Parameter	Trial 1			Trial 2		
	26-Week analysis (*N* = 17)	1-Year analysis[a] (*N* = 17)	2-Year analysis[b] (*N* = 17)	26-Week analysis (*N* = 20)	1-Year analysis[a] (*N* = 20)	2-Year analysis[b] (*N* = 20)
Primary end points						
Mean change from baseline in platelet count, $\times 10^9$/l (95% CI)	73[c] (40–105)	91[c] (67–116)[d]	75[c] (54–96)	NA	NA	NA
Normalization of platelet count, *n/N* (%)	14/17 (82)	15/17 (88)	15/17 (88)	18/20 (90)	18/20 (90)	18/20 (90)
TMA event-free status, *n/N* (%)	15/17 (88)	15/17 (88)	15/17 (88)	16/20 (80)	17/20 (85)	19/20 (95)
Hematologic normalization, *n/N* (%)	13/17 (76)	15/17 (88)	15/17 (88)	18/20 (90)	18/20 (90)	18/20 (90)
Secondary end points						
TMA and hematologic outcomes						
Complete TMA response, *n/N* (%)	11/17 (65)	13/17 (76)	13/17 (76)	5/20 (25)	7/20 (35)	11/20 (55)
LDH ⩽ ULN, *n/N* (%)	14/17 (82)	15/17 (88)	15/17 (88)	19/20 (95)	19/20 (95)	19/20 (95)
Increase in hemoglobin concentration of ⩾20 g/l from baseline, *n/N* (%)	11/17 (65)	13/17 (76)	13/17 (76)	9/20 (45)	10/20 (50)	13/20 (65)
Mean change in haptoglobin level from baseline, g/l (s.d.)	0.5 (0.44)	0.6 (0.41)	0.9 (0.38)	−0.1 (0.52)	0.3 (0.61)	0.5 (0.64)
Renal outcomes						
Increase in eGFR of ⩾15 ml/min per 1.73 m^2, *n/N* (%)[e]	8/17 (47)	9/17 (53)	10/17 (59)	1/20 (5)	3/20 (15)	8/20 (40)
Decrease in serum creatinine level of ⩾25%, *n/N* (%)[e]	11/17 (65)	13/17 (76)	13/17 (76)	3/20 (15)	7/20 (35)	11/20 (55)
Improvement in proteinuria by ⩾1 grade, *n/N* (%)[e,f]	12/16 (75)	13/16 (81)	14/16 (88)	6/11 (55)	7/11 (64)	9/11 (82)
Improvement in CKD by ⩾1 stage, *n/N* (%)[e]	10/17 (59)	11/17 (65)	12/17 (71)	7/20 (35)	9/20 (45)	12/20 (60)

Riduzione Rischio di ESRD
dal 60-70% a circa il 15-20% negli adulti e
dal 30-40% a circa il 5-10% nei bambini.

Mortalità a 3-5 aa di CM-HUS in era pre-eculizumab = 8-14% bambini e 2-4% negli adulti, praticamente quasi azzerata

trattamento di prima linea e deve essere somministrato prima possibile, comunque entro 24-48 ore dall'esordio, una volta esclusa la PTT e la STEC-HUS, anche prima nei pazienti con storia familiare di CM HUS e nei casi di recidiva post trapianto di rene e non si deve aspettare alcun esame genetico

sopprimendo la via terminale del complemento, aumenta in maniera significativa il rischio d'infezione meningococcica e da batteri capsulati>>
vaccinazione contro il meningococco (vaccino coniugato tetravalente A, C, W 135, Y e il vaccino per il sierogruppo B) *almeno 2 settimane prima dell'inizio della terapia*, Streptococcus Pneumoniae e Haemophilus Influenzae B
profilassi antibiotica (ciprofloxacina, ceftriaxone, penicillina, amoxi cillina) da proseguire durante tutto il trattamento per immunodepressi o <6aa o per almeno le prime 2 settimane dopo la vaccinazione

Peso corporeo del paziente	Fase iniziale	Fase di mantenimento
da 30 a 40 kg	600 mg alla settimana per le prime 2 settimane	900 mg alla settimana 3; poi 900 mg ogni 2 settimane
da 20 a < 30 kg	600 mg alla settimana per le prime 2 settimane	600 mg alla settimana 3; poi 600 mg ogni 2 settimane
da 10 a < 20 kg	600 mg in dose singola alla settimana 1	300 mg alla settimana 2; poi 300 mg ogni 2 settimane
da 5 a < 10 kg	300 mg in dose singola alla settimana 1	300 mg alla settimana 2; poi 300 mg ogni 3 settimane

adulti (≥ 18 anni) e > 40 Kg :

fase iniziale di 4 settimane seguita da una fase di mantenimento:

- **Fase iniziale: 900 mg di Soliris somministrati con un'infusione endovenosa di 45 minuti ogni settimana per le prime 4 settimane.**
- **Fase di mantenimento: 1200 mg di Soliris somministrati con un'infusione endovenosa di 45 minuti nella quinta settimana, seguita da 1200 mg di Soliris somministrati con un'infusione endovenosa di 45 minuti ogni 14 giorni**

In caso di concomitante plasmaferesi (PF), scambio plasmatico (SP) o infusione di plasma (IP) fresco congelato è necessaria una dose supplementare di Soliris secondo lo schema illustrato di seguito:

Tipo di intervento con plasma	Dose di Soliris più recente	Dose supplementare di Soliris per ogni intervento con PF/SP/IP	Tempistica della somministrazione della dose supplementare di Soliris
Plasmaferesi o scambio plasmatico	300 mg	300 mg per ogni plasmaferesi o sessione di scambio plasmatico	Entro 60 minuti dopo ogni plasmaferesi o scambio plasmatico
	≥ 600 mg	600 mg per ogni plasmaferesi o sessione di scambio plasmatico	
Infusione di plasma fresco congelato	≥ 300 mg	300 mg per infusione di plasma fresco congelato	60 minuti prima di ogni infusione di plasma fresco congelato

RAVULIZUMAB, long-acting C5 complement inhibitor

RAVULIZUMAB

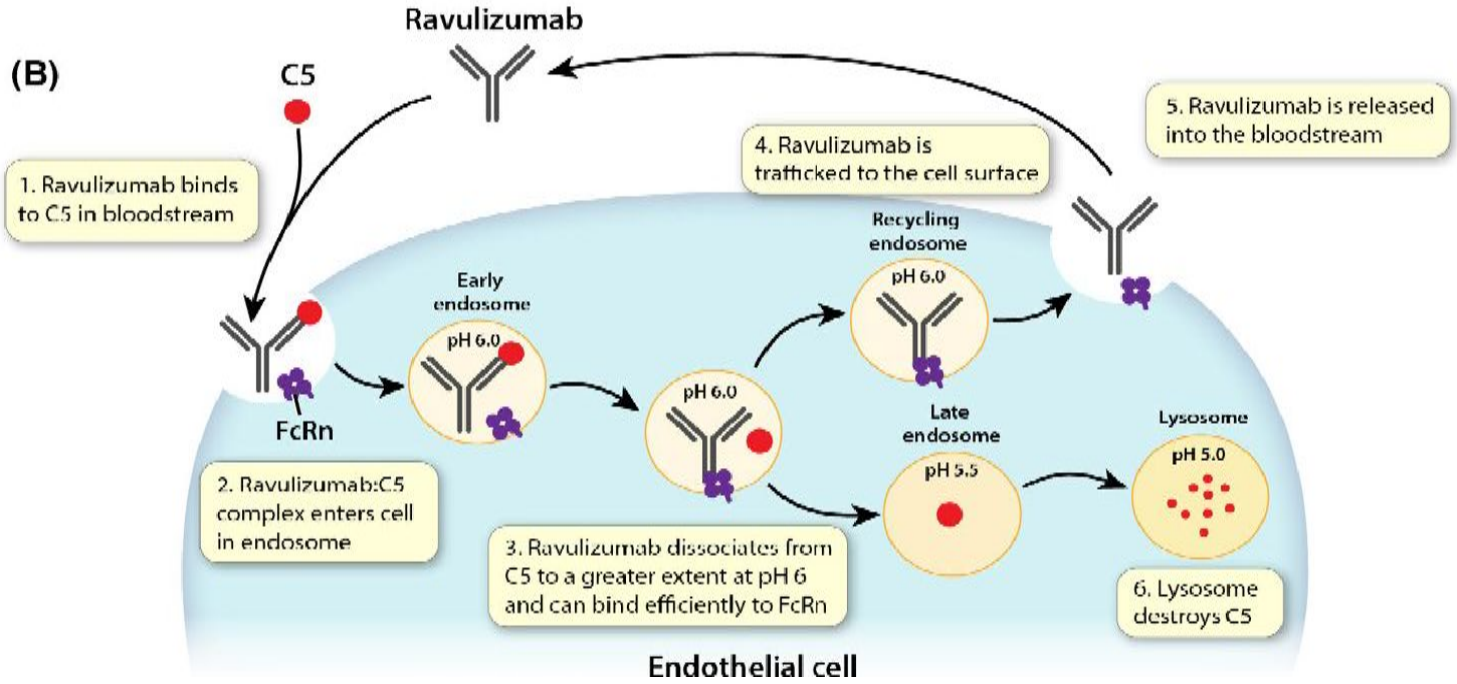
- Humanized anti-C5 monoclonal antibody targeting terminal complement activation at C5†[1-3]
- Immediate, complete, and sustained C5 inhibition[3,6-13]
- Intravenous infusion†
  (100 mg/mL formulation)[1,4,9,13]
- Weight-based, ***up to 8-week (Q8W) dosing regimen***[4,7,13]
- Generally well tolerated, with no unexpected safety concerns[10-13]

SERIOUS RISK OF MENINGOCOCCAL INFECTIONS

According to ACIP recommendations, patients should be immunised with meningococcal vaccines at least 2 weeks prior to administering the first dose of RAVULIZUMAB, unless the risks of delaying RAVULIZUMAB therapy outweigh the risks of developing a meningococcal infection[4]

1. Sahelijo L et al. Blood. 2015;126(23):4777-; 2. Sheridan D et al. PLoS One. 2018;13(4):e0195909; 3. Risitano AM et al. Biologics. 2008 Jun;2(2):205-22; 4. Alexion. https://alexion.com/documents/ultomiris_uspi. Accessed: 15th November 2021; 5. FDA.https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125166s431lbl.pdf. Accessed: 06th October 2020; 6. Lee JW et al. Blood. 2019 Feb 7;133(6):530-9; 7. Kulasekararaj AG et al. Blood. 2019 Feb 7;133(6):540-9; 8. Risitano AM et al. Am J Hematol. 2018 Aug;93(4):564-77; 9. EMA. https://www.ema.europa.eu/en/documents/product-information/ultomiris-epar-product-information_en.pdf; 10. Rondeau E et al. Kidney International. 2020;97(6):1287-96; 11. Ariceta G, et al. Kidney International. 2021;100:225–237. 12. Tanaka K, et al. Pediatric Nephrology. 2021;36(4):889-98. 13. Syed YY. Drugs. 2021;81(5):587-94. 14. Peipert JD et al. PLOS ONE. 2020;15(9):e0237497
ACIP, Advisory Committee on Immunization Practices; EMA, European Medicines Agency; FDA, Food and Drug Administration; PDUFA, Prescription Drug User Fee Act; Q8W, every eight weeks.

RAVULIZUMAB, long-acting C5 complement inhibitor



Dixon BP, et al. J Clin Pharm Ther. 2022;47:1081–87

RAVULIZUMAB – Clinical Studies

RAVULIZUMAB

Phase III, open-label, single-treatment arm, multicentre trials

ALXN1210-aHUS-311

Adults (≥18 years) with documented diagnosis of aHUS, **naïve to C5-complement inhibitors**[1]

ALXN1210-aHUS-312

Pediatric patients (from birth up to <18 years) with diagnosis of aHUS
Cohort 1: **naïve to treatment with C5-complement inhibitors**
Cohort 2: **eculizumab-experienced patients**

Primary objective: evaluate the efficacy of ravulizumab to inhibit complement-mediated TMA

Primary efficacy endpoint: complete TMA response‡ during the initial 26-week treatment evaluation period

Criteria for complete TMA response: normalisation of hematological parameters (platelet count and LDH) and ≥25% improvement in sCr from baseline.
Rondeau E et al. Kidney International. 2020;97(6):1287-96; Barbour T et al. Kidney Int Rep. 2021;6(6):1603-13; Ariceta G et al. Kidney Int 2021;100(1):225–237; Tanaka K et al. Pediatr Nephrol 2021;36(4):889-898.
aHUS, atypical hemolytic uremic syndrome; TMA, thrombotic microangiopathy.

1. **Dose di carico a tempo zero**
2. **Dopo due settimane prima dose di mantenimento di Ravulizumab, ripetuta poi**
   a. **una volta ogni 8 settimane per i pazienti con peso superiore a 20 kg e**
   b. **ogni 4 settimane per i pazienti con peso inferiore a 20 kg.**

Tutte le infusioni in SF devono durare circa 2 ore

Intervallo di peso corporeo (kg)	Dose di carico (mg)	Dose di mantenimento (mg)
da 10 a meno di 20ª	600	600
da 20 a meno di 30ª	900	2100
da 30 a meno di 40ª	1200	2700
da 40 a meno di 60	2400	3000
da 60 a meno di 100	2700	3300
più di 100	3000	3600

peso corporeo (kg)	ravulizumab più recente (mg)	(mg) dopo ogni intervento di SP o PP	(mg) dopo il termine di un ciclo di IVIg
da ≥ 40 a < 60	2400	1200	600
	3000	1500	
da ≥ 60 a < 100	2700	1500	600
	3300	1800	
≥ 100	3000	1500	600
	3600	1800	
Tempistica della dose supplementare di ravulizumab		Entro 4 ore dopo ogni intervento di SP o PP	Entro 4 ore dal termine di un ciclo di IVIg

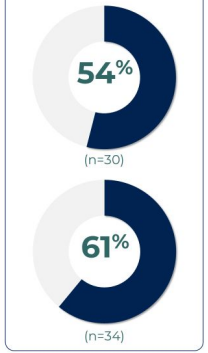
Sigle: IVIg = immunoglobulina per via endovenosa; kg = chilogrammo; SP scambio plasmatico; PP = plasmaferesi.

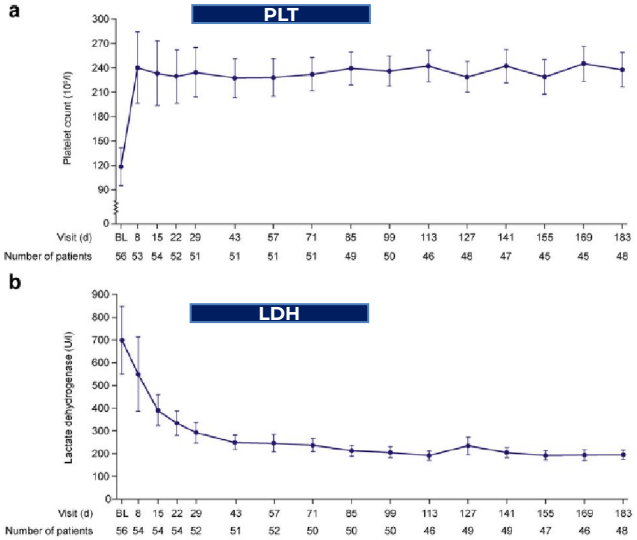
In mantenimento anche sc

RAVULIZUMAB – ALXN1210-aHUS-311 – Efficacy

Adult data

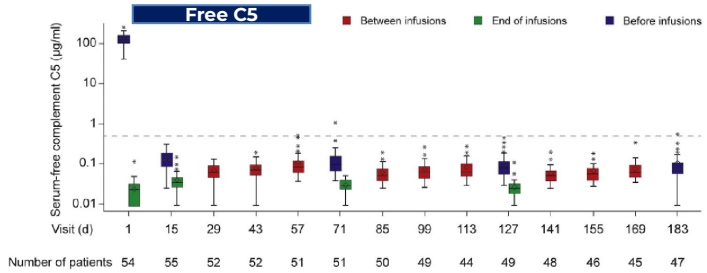
Complete TMA Response





eGFR categories at baseline (N=47)[a]		eGFR categories at day 183					
		1 (≥90)	2 (60–89)	3a (45–59)	3b (30–44)	4 (15–29)	5 (<15)
1 (≥90)	0 (0.0)						
2 (60–89)	3 (6.4)	2 (4.3)	1 (2.1)				
3a (45–59)	1 (2.1)	1 (2.1)					
3b (30–44)	2 (4.3)	2 (4.3)					
4 (15–29)	7 (14.9)	1 (2.1)			3 (6.4)	1 (2.1)	2 (4.3)
5 (<15)	34 (72.3)	6 (12.8)	6 (12.8)	3 (6.4)	3 (6.4)	5 (10.6)	11 (23.4)

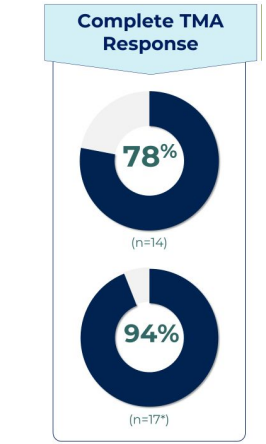
~50% (27/56) of adults in the Phase III ravulizumab trial program received treatment while in **the ICU**

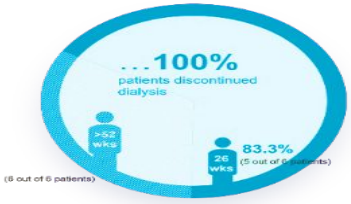


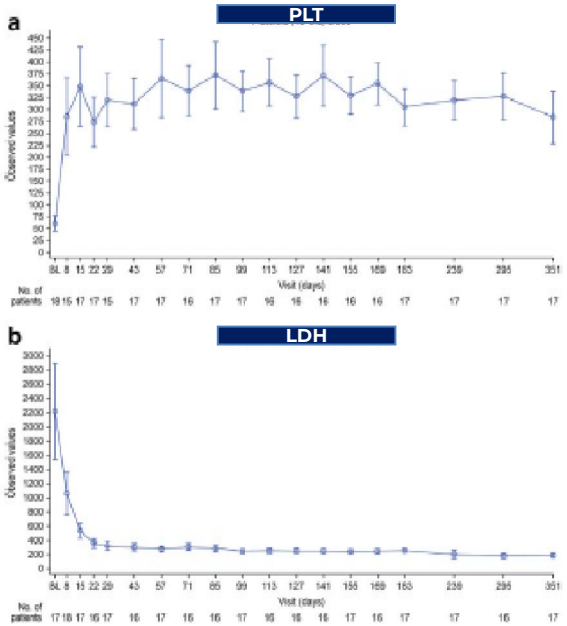
Rondeau E et al. Kidney International. 2020;97(6):1287-96; Barbour T et al. Kidney Int Rep. 2021;6(6):1603-13.
aHUS, atypical hemolytic uremic syndrome; eGFR = estimated glomerular filtration rate; LDH, = lactate dehydrogenase; PLT = platelet; TMA, thrombotic microangiopathy.

RAVULIZUMAB – ALXN1210-aHUS-312 – Efficacy

Paediatric data







a

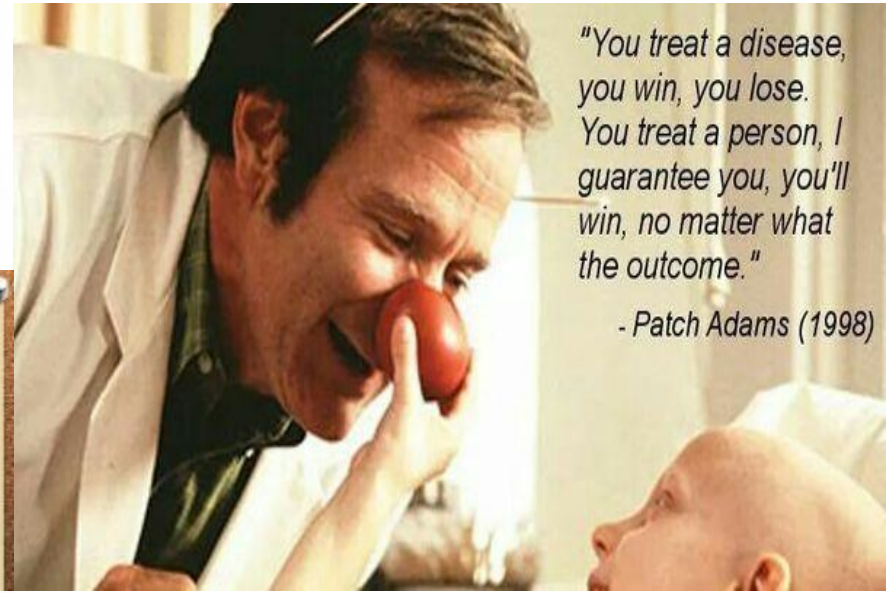
eGFR categories at baseline (N = 17)		eGFR categories at week 26					
		1 (≥90)	2 (60–89)	3a (45–59)	3b (30–44)	4 (15–29)	5 (<15)
1 (≥90)	0						
2 (60–89)	1 (5.9)	1 (5.9)					
3a (45–59)	1 (5.9)	1 (5.9)					
3b (30–44)	1 (5.9)	1 (5.9)					
4 (15–29)	8 (47.1)	5 (29.4)	1 (5.9)	1 (5.9)		1 (5.9)	
5 (<15)	6 (35.3)	3 (17.6)	2 (11.8)				1 (5.9)

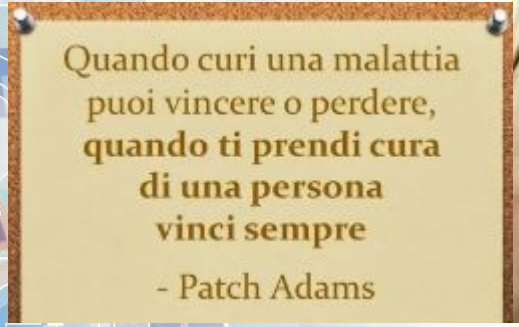
b

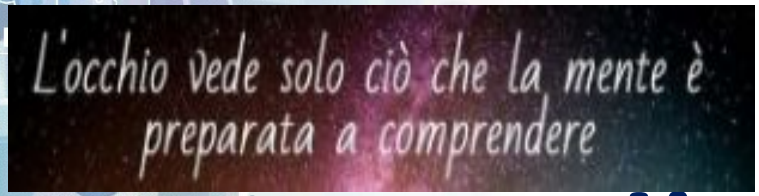
eGFR categories at baseline (N = 16)		eGFR categories at week 50					
		1 (≥90)	2 (60–89)	3a (45–59)	3b (30–44)	4 (15–29)	5 (<15)
1 (≥90)	0						
2 (60–89)	1 (6.3)	1 (6.3)					
3a (45–59)	1 (6.3)	1 (6.3)					
3b (30–44)	1 (6.3)	1 (6.3)					
4 (15–29)	8 (50.0)	6 (37.5)		1 (6.3)	1 (6.3)		
5 (<15)	5 (31.3)	3 (18.8)	1 (6.3)	1 (6.3)			

Ariceta G et al. Kidney Int 2021;100(1):225–237; Tanaka K et al. Pediatr Nephrol 2021;36(4):889-898.
aHUS, atypical hemolytic uremic syndrome; eGFR = estimated glomerular filtration rate; LDH, = lactate dehydrogenase; PLT = platelet; ICU, intensive care unit; TMA, thrombotic microangiopathy.

#FIERIDIVOI
#FIERIDIMEU







#GUARDAOLTRE

Grazie per l'attenzione