Sociedad Médica de Santiago
Sociedad Chilena de Medicina Interna
150 años al Servicio de la Medicina

IX CURSO MEDICINA INTERNA HOSPITALARIA 2019

MICROAGIOPATIAS TROMBOTICAS

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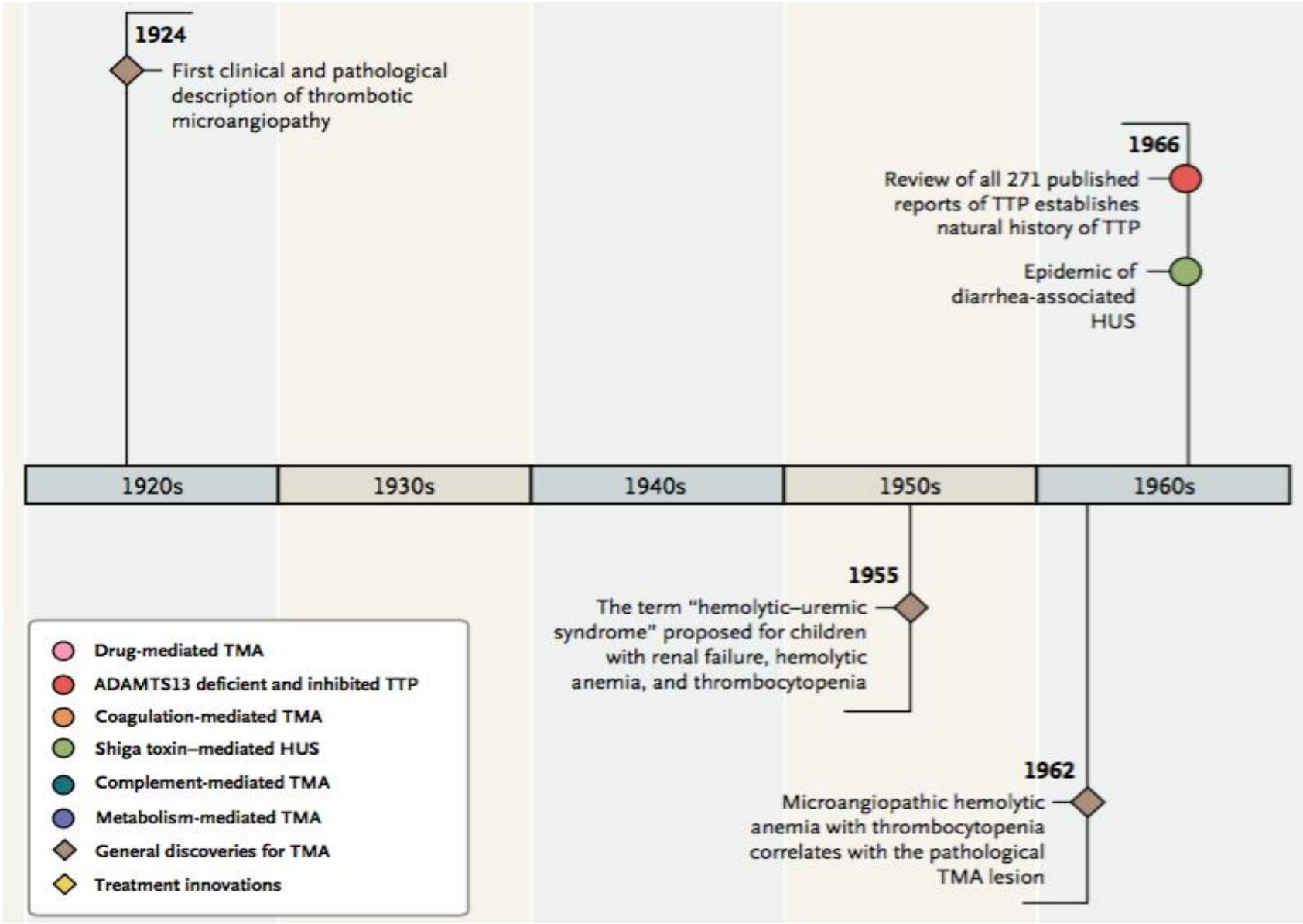
DEFINICION

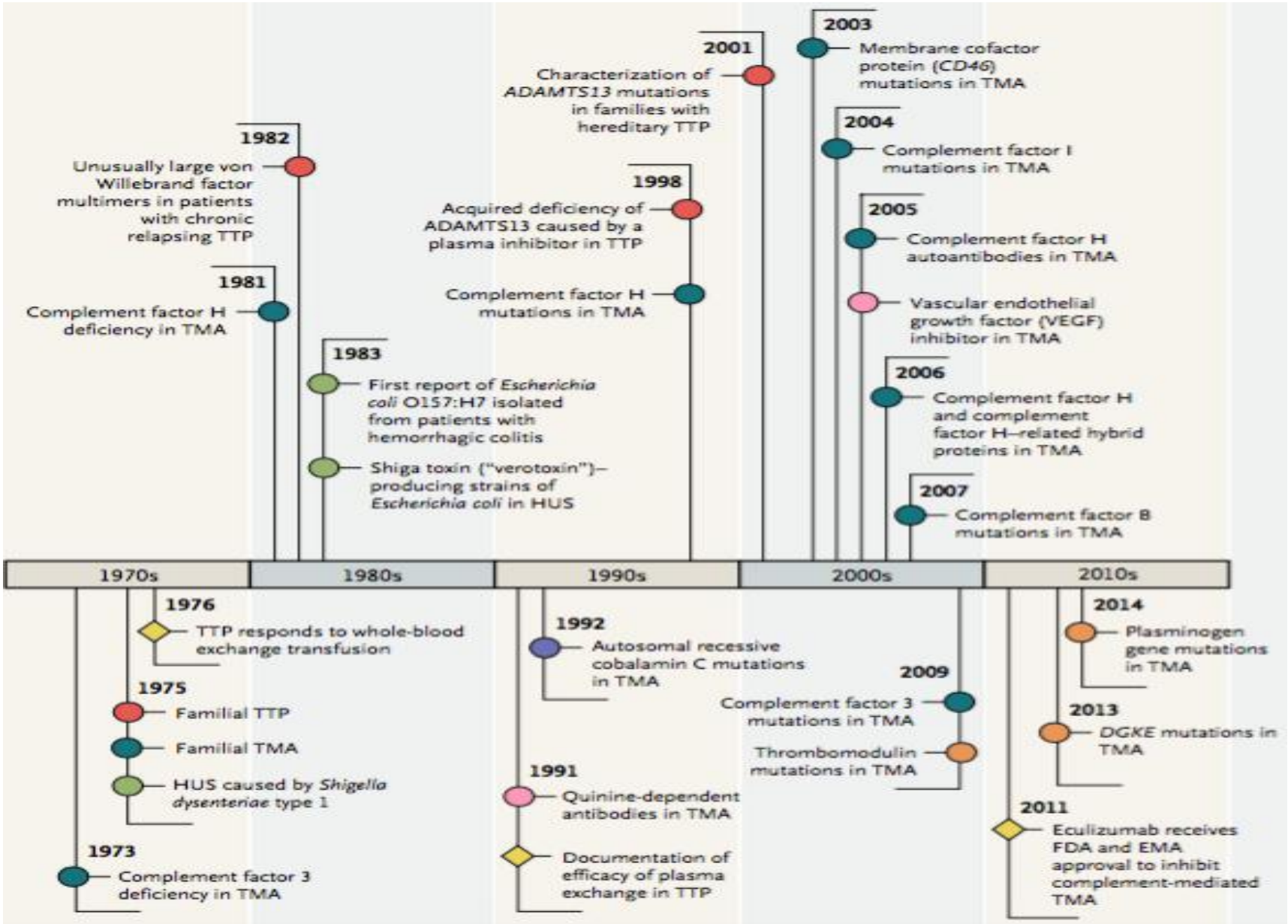
Conjunto de enfermedades que poseen en común:

- *ANEMIA NORMO NORMO*
- *HEMOLITICA INTRA-VASCULAR* (extra-corposcular) *NO INMUNE* (coombs negativo)
- *TROMBOCITOPENIA*

ANEMIAS MICROANGIOPATICAS TROMBOTICAS (AHMA + trombosis)

ANEMIAS HEMOLITICA MICROANGIOPATICAS y TROMBOCITOPENIA


1924
First clinical and pathological description of thrombotic microangiopathy
1966
Review of all 271 published reports of TTP establishes natural history of TTP
Epidemic of diarrhea-associated HUS
1920s
1930s
1940s
1950s
1960s
1955
The term "hemolytic–uremic syndrome" proposed for children with renal failure, hemolytic anemia, and thrombocytopenia
1962
Microangiopathic hemolytic anemia with thrombocytopenia correlates with the pathological TMA lesion
Drug-mediated TMA
ADAMTS13 deficient and inhibited TTP
Coagulation-mediated TMA
Shiga toxin–mediated HUS
Complement-mediated TMA
Metabolism-mediated TMA
General discoveries for TMA
Treatment innovations


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

EPIDEMIOLOGIA

SHU representa la **3ª causa de injuria renal aguda en pediatría y la 3ª de ERC** (Chile)

Estudio chileno de PPT (18 casos):
Aspectos clínicos:

- edad promedio fue de 53 ± 21 años (15-81 años), neoplasia (17%), síntoma neurológico (83%),
- fiebre (28%), 1 calofríos (6%), 7 dolor abdominal (39%), 4 dolor lumbar (22%), náuseas o vómitos (17%), 4 pigmenturia macroscópica (22%) y 2 epistaxis (22%), petequias o equimosis (22%).

Laboratorio:

- hematocrito bajo 30% (78%), leucocitosis mayor a 11.000/mm^3 en 8 casos (44%), y leucopenia menor a 4.500/mm^3 (22%)
- desviación izquierda (más de 5% de formas inmaduras) (57%)., 100% presentó trombocitopenia, VHS promedio fue de 54
- 100% tenía LDH elevada en promedio 1.566 mg/dl ±1.286 (290-5.296) y bilirrubina total elevada (89%), con un promedio de 2,7 mg/dl ± 1,7 (0,55-6,7).
- 12 pacientes se les solicitó haptoglobina, siendo menor a 5,8 en 11 de éstos.
- En todos los casos la prueba de Coombs directa fue negativa.
- De los 17 pacientes que se les midió actividad de metaloproteinasa de FVW, nivel bajo el punto de corte normal (88%) y presencia de inhibidor (80%).

Púrpura trombótico trombocitopénico: Revisión de la literatura a partir de 18 casos, Rev Méd Chile 2008; 136: 1518-1527

ETIOLOGIAS y CLASIFICACION

ANEMIA HEMOLITICA MICROANGIOPATICA TROMBOTICA PRIMARIA

AMAT HEREDITARIA

- Déficit del ADAMST13
- Mediado por complemento
- Mediado por metabolismo *(alteración vit B 12 y ácido fólico, por mutaicón gen del MMACHC (MethylMalonic Aciduria and Homocystinuria type C)*
- Mediado por la coagulación *por mutación gen del plasminógeno, trombomodulina, DGKE*

AMAT ADQUIRIDAS

- Déficit del ADAMST13
- Mediado por toxina Shiga
- Mediado por drogas (mecanismo inmune) *= quinidina, gemcitabina, oxaliplatino y quetiapina*
- Mediado por drogas (mecanismo tóxico) *= gemcitabina, ciclosporina, tacrolimus, sirolimus, bevacisumab.*
- Mediado por complemento (CID)

ANEMIA HEMOLITICA NO INMUNE MICROANGIOPATICAS

REUMATOLOGICAS
Lupus Eritematoso Sistémico
Esclerosis sistémica
Sindrome Antifosfolípido.

INFECCIONES
Malaria
Babesiosis
Sepsis por clostridium perfringens
Bartonellosis
Endocarditis infecciosa
VIH, CMV, Fiebre montaña rocallosas
Aspergilosis

OTROS AGENTES
Quimicos
Drogas
Venenos
Quemaduras extensas

ANEMIA HEMOLITICA MACRO ANGIOPATICA
Válvulas cardiácas
Hemoglobinuria inducida por ejercicio

ONCOLOGICOS (tumores sólidos y hematológicos)

Transplante de órganos sólidos o TPH

CLINICA y EXAMENES DIAGNOSTICOS

Palidez – Púrpura – Fiebre - oliguria

Compromiso de conciencia, convulsiones

EXAMENES de HEMOLISIS
HEMOGRAMA = ANEMIA + TROMBOCITOPENIA

FROTIS de SANGRE PERIFERICA = ESQUIZTOCITOS

LDH AUMENTADA

BILIRRIBUNA INDERECTA AUMENTADA

HAPTOGLOBINA BAJA

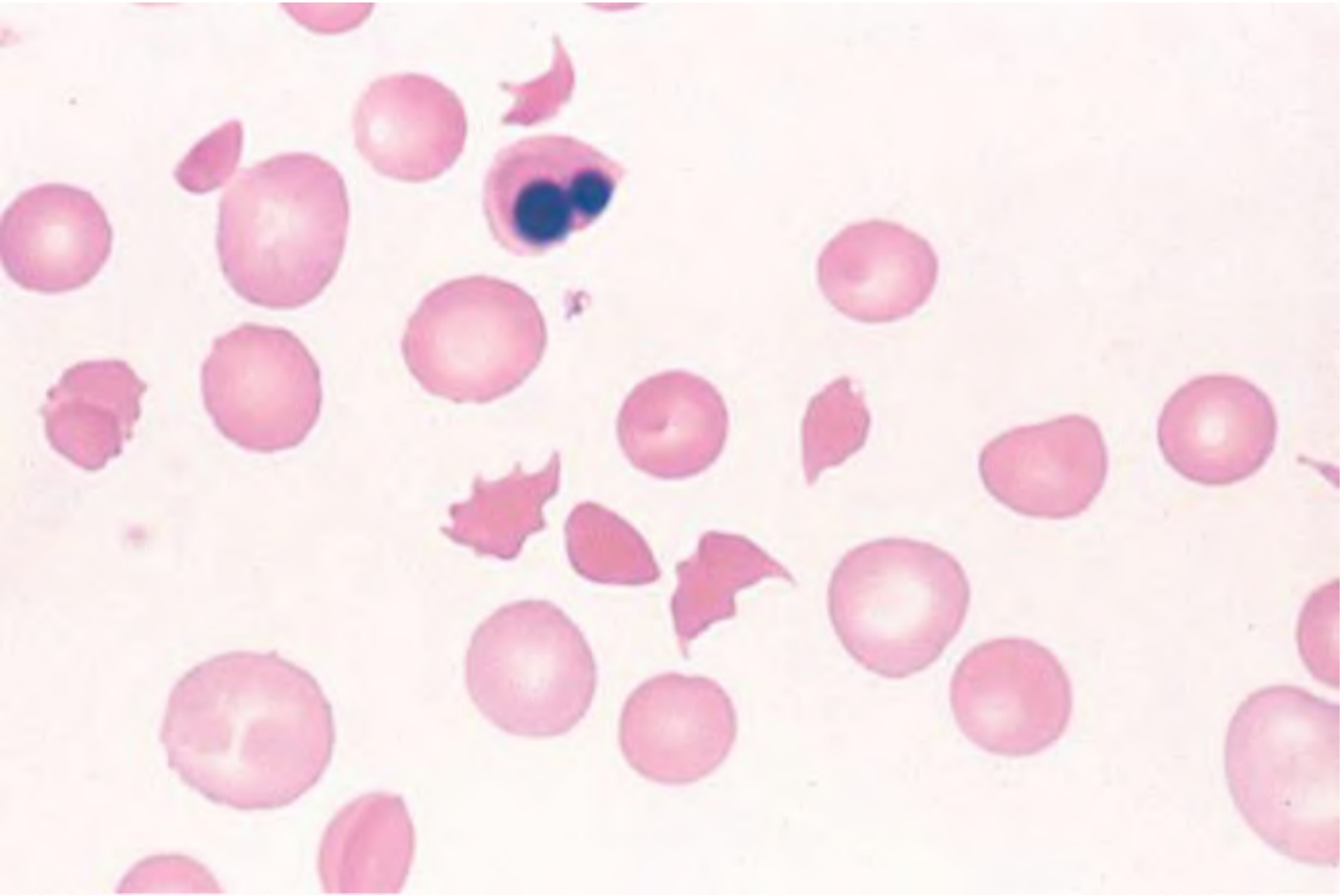
EXAMENES de AMAT
ACTIVIDAD (ADAMTS13) (< 10%)

INHIBIDOR de la METALOPROTEASA

FIBRINOGENO

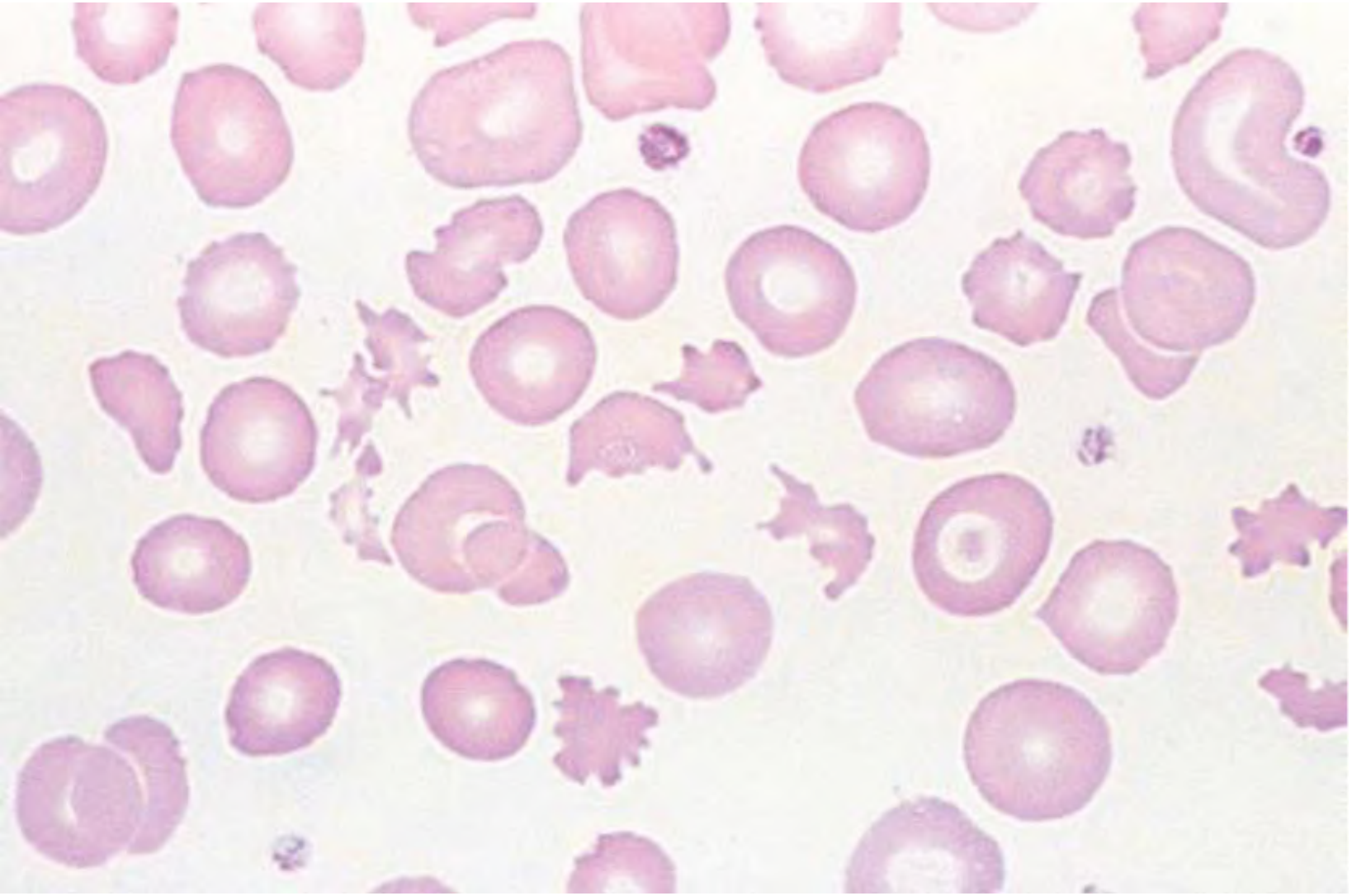
HOMOCISTEINEMIA y MMA sérica

Coprocultivo



Presencia de esquistocitos y reticulocito, disminución de plaquetas.

(AHMA en paciente con PTT).



Presencia de esquistocitos y reticulocito, disminución de plaquetas.

(AHMA por valvula cardiaca protésica)

FISIOPATOLOGIA

AMAT HEREDITARIA

- Déficit del ADAMST13
- Mediado por complemento
- Mediado por metabolismo *(alteración vit B 12 y ácido fólico)*
- Mediado por la coagulación (CID) *por mutación gen del plasminógeno, trombomodulina, DGKE*

AMAT ADQUIRIDAS

- Déficit del ADAMST13
- Mediado por toxina Shiga
- Mediado por drogas (mecanismo inmune) *= quinidina, gemcitabina, oxaliplatino y quetiapina*
- Mediado por drogas (mecanismo tóxico) *= gemcitabina, ciclosporina, tacrolimus, sirolimus, bevacisumab.*
- Mediado por complemento

ADAMTS13 Deficiency–Thrombotic Thrombocytopenic Purpura (TTP)

Cause	Clinical Features	Initial Management
Homozygous (or compound heterozygous) *ADAMTS13* mutations	Initial presentation typically in children but may also present in adults; may have evidence of ischemic organ injury; acute kidney injury is uncommon; patients with heterozygous mutations are asymptomatic	Plasma infusion

Complement-Mediated TMA

Cause	Clinical Features	Initial Management
Mutations of *CFH*, *CFI*, *CFB*, *C3*, or *CD46* causing uncontrolled activation of the alternative pathway of complement	Initial presentation most often in children but may also present in adults; acute kidney injury is common; patients with heterozygous mutations may be symptomatic	Plasma infusion or exchange, anti-complement agent

Metabolism-Mediated TMA

Cause	Clinical Features	Initial Management
Homozygous mutations of *MMACHC* (methylmalonic aciduria and homocystinuria type C protein) gene	Typically in children <1 yr of age; also reported in a young adult with hypertension, AKI	Vitamin B_{12}, betaine, folinic acid

Coagulation-Mediated TMA

Cause	Clinical Features	Initial Management
Homozygous mutations in *DGKE*; mutations in *PLG* and *THBD* are also implicated	*DGKE* mutations: initial presentation with AKI, typically in children <1 yr of age; clinical features of other disorders have not been described	Plasma infusion

ADAMTS13 Deficiency–Thrombotic Thrombocytopenic Purpura (TTP)

Cause	Clinical Features	Initial Management
Autoantibody inhibition of ADAMTS13 activity	Uncommon in children; often with evidence of ischemic organ injury; acute kidney injury is uncommon	Plasma exchange, immunosuppression

Shiga Toxin

Cause	Clinical Features	Initial Management
Enteric infection with a Shiga toxin–secreting strain of *Escherichia coli* or shigella	More common in young children, typically with acute kidney injury; most cases occur in regions where Shiga toxin is endemic, although large outbreaks also occur	Supportive care

Drug (Immune)

Cause	Clinical Features	Initial Management
Caused by quinine and possibly other drugs; drug-dependent antibodies affect multiple cells	Sudden onset of severe systemic symptoms with anuric acute kidney injury	Removal of drug; supportive care

Drug (Toxic)

Cause	Clinical Features	Initial Management
Caused by multiple drugs; VEGF inhibition in kidney podocytes is one example	Gradual onset of renal failure over weeks or months	Removal of drug; supportive care

Acquired Complement

Cause	Clinical Features	Initial Management
Antibody inhibition of CFH activity	Initial presentation with AKI in children or adults	Plasma exchange, immunosuppression, anti-complement agent

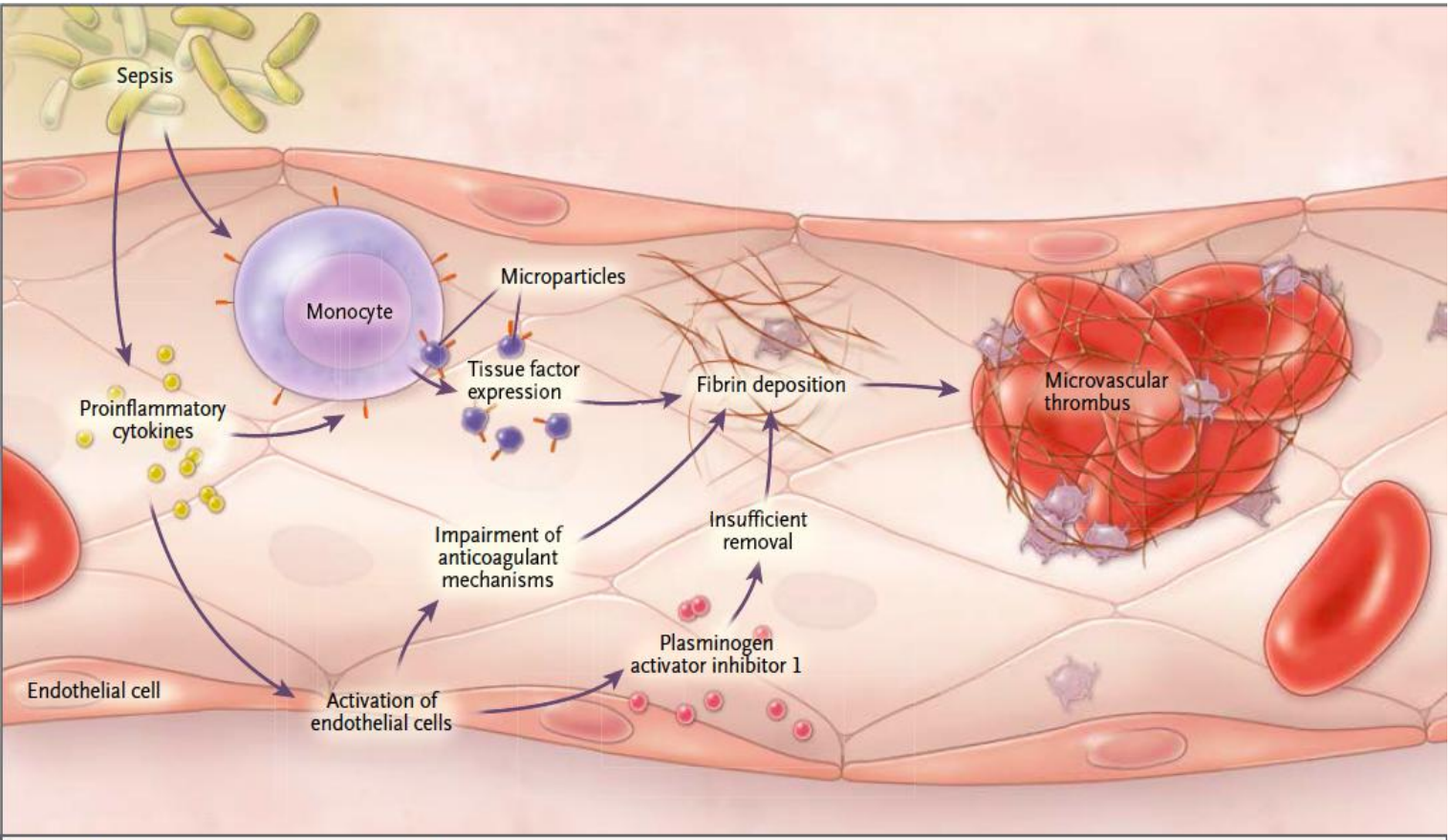


Figure 2. Pathogenesis of Disseminated Intravascular Coagulation in Sepsis.

Through the generation of proinflammatory cytokines and the activation of monocytes, bacteria cause the up-regulation of tissue factor as well as the release of microparticles expressing tissue factor, thus leading to the activation of coagulation. Proinflammatory cytokines also cause the activation of endothelial cells, a process that impairs anticoagulant mechanisms and down-regulates fibrinolysis by generating increased amounts of plasminogen activator inhibitor.

Exposición de FT→ Generación de Trombina

Amplificación de la generación de Trombina→ Mecanismos anticoagulantes fisiológicos defectuosos

Propagación de los depósitos de fibrina→ Deficiencia de la fibrinolisis

Table 2. Diagnostic Scoring System for Disseminated Intravascular Coagulation (DIC).*

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

- If yes, proceed with this algorithm
- If no, do not use this algorithm

Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related marker)

Score the test results as follows:

- Platelet count: 50,000 to 100,000 per mm^3, 1 point; <50,000 per mm^3, 2 points
- Elevated fibrin-related marker (e.g., D-dimer, fibrin degradation products): no increase, 0 points; moderate increase, 2 points; strong increase, 3 points
- Prolonged prothrombin time: <3 sec, 0 points; ≥3 sec but <6 sec, 1 point; ≥6 sec, 2 points
- Fibrinogen level: ≥1 g per liter, 0 points; <1 g per liter, 1 point

Calculate the score as follows:

- ≥5 points: compatible with overt DIC; repeat scoring daily
- <5 points: suggestive of nonovert DIC; repeat scoring within next 1 to 2 days

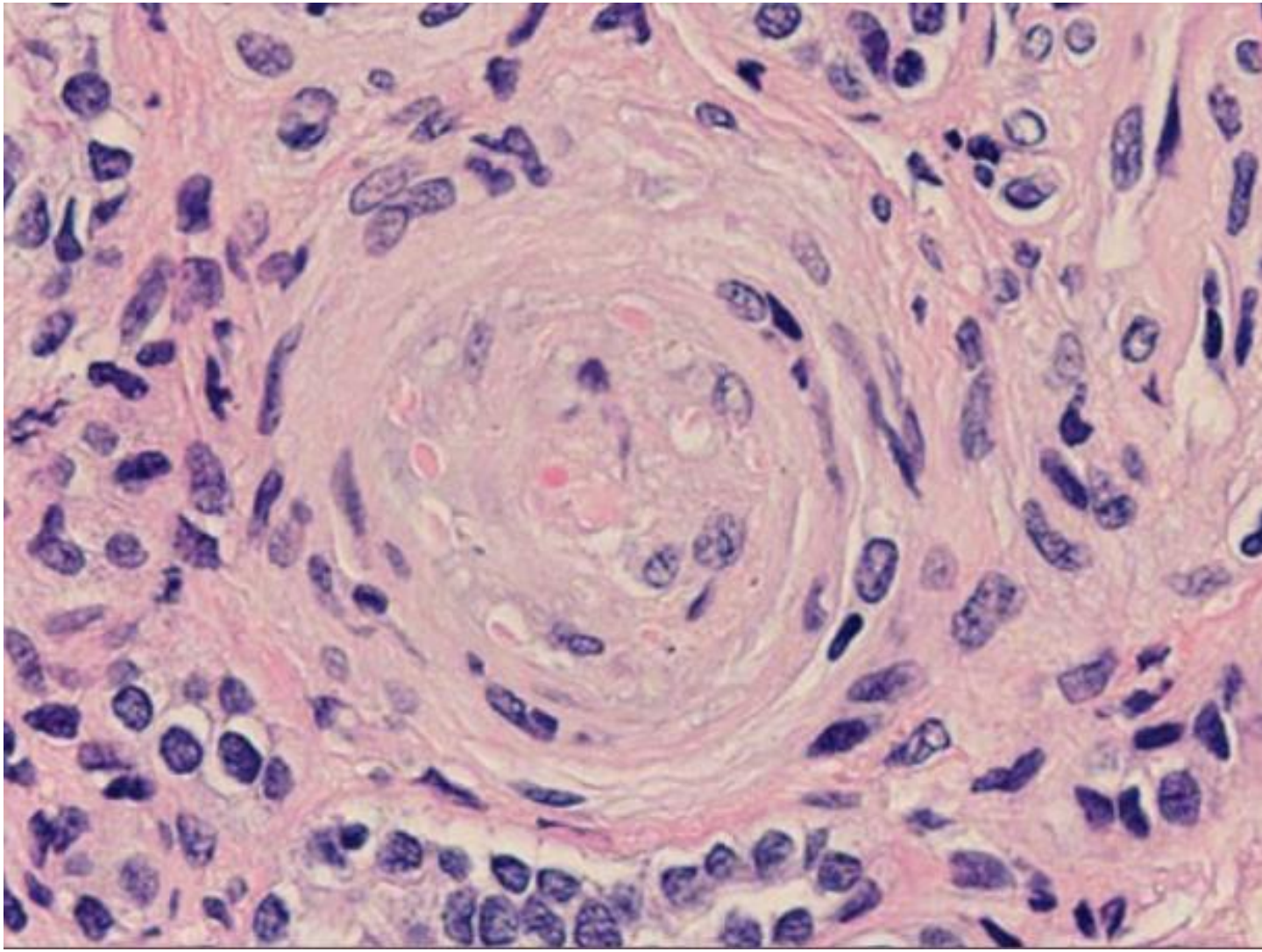
* Data are adapted from Toh and Hoots[21] on the basis of the scoring system developed by the International Society on Thrombosis and Hemostasis.

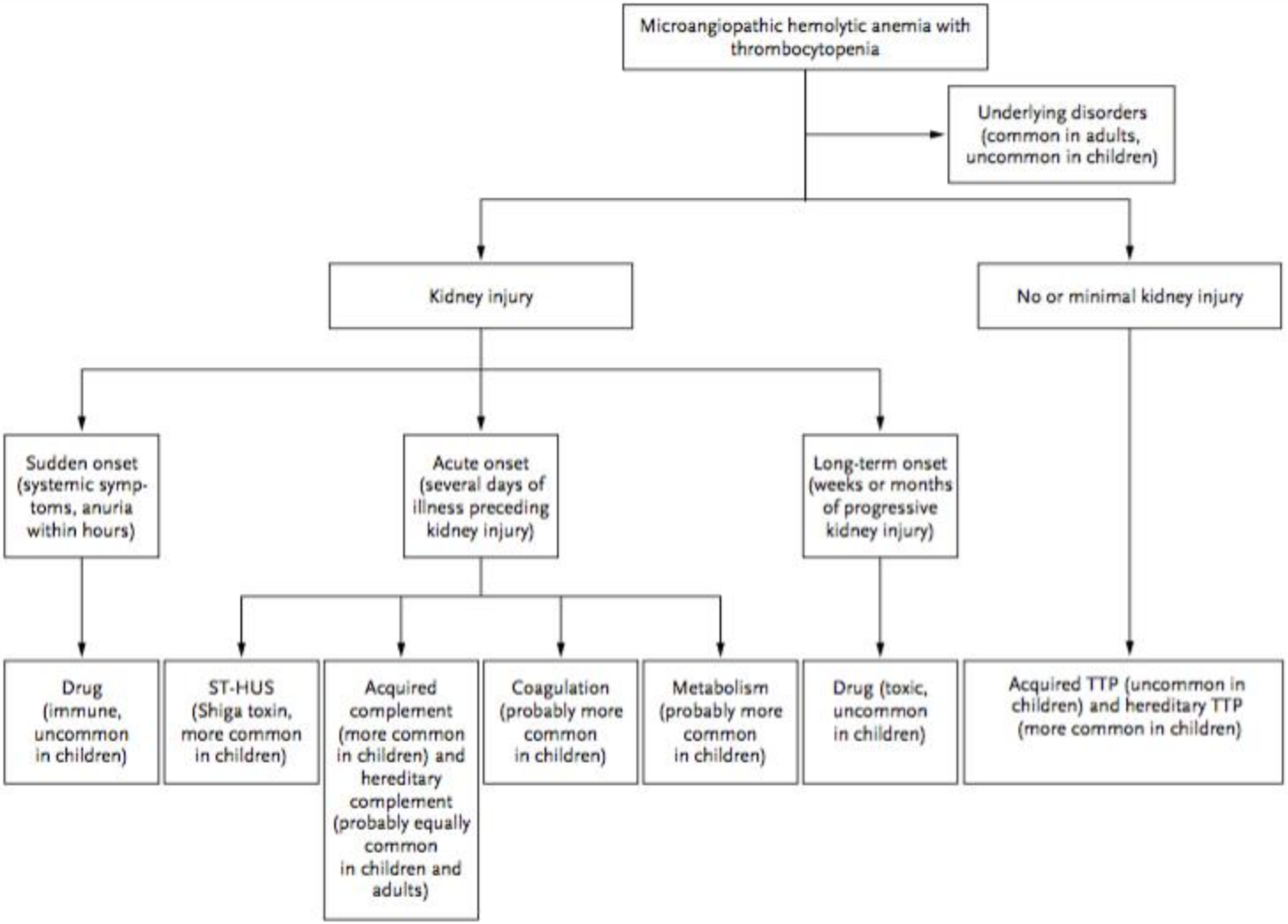
En las AHMA trombóticas presentan a nivel histológico un mecanismo de daño común que es la alteración vascular a nivel de las arteriolas y capilares.

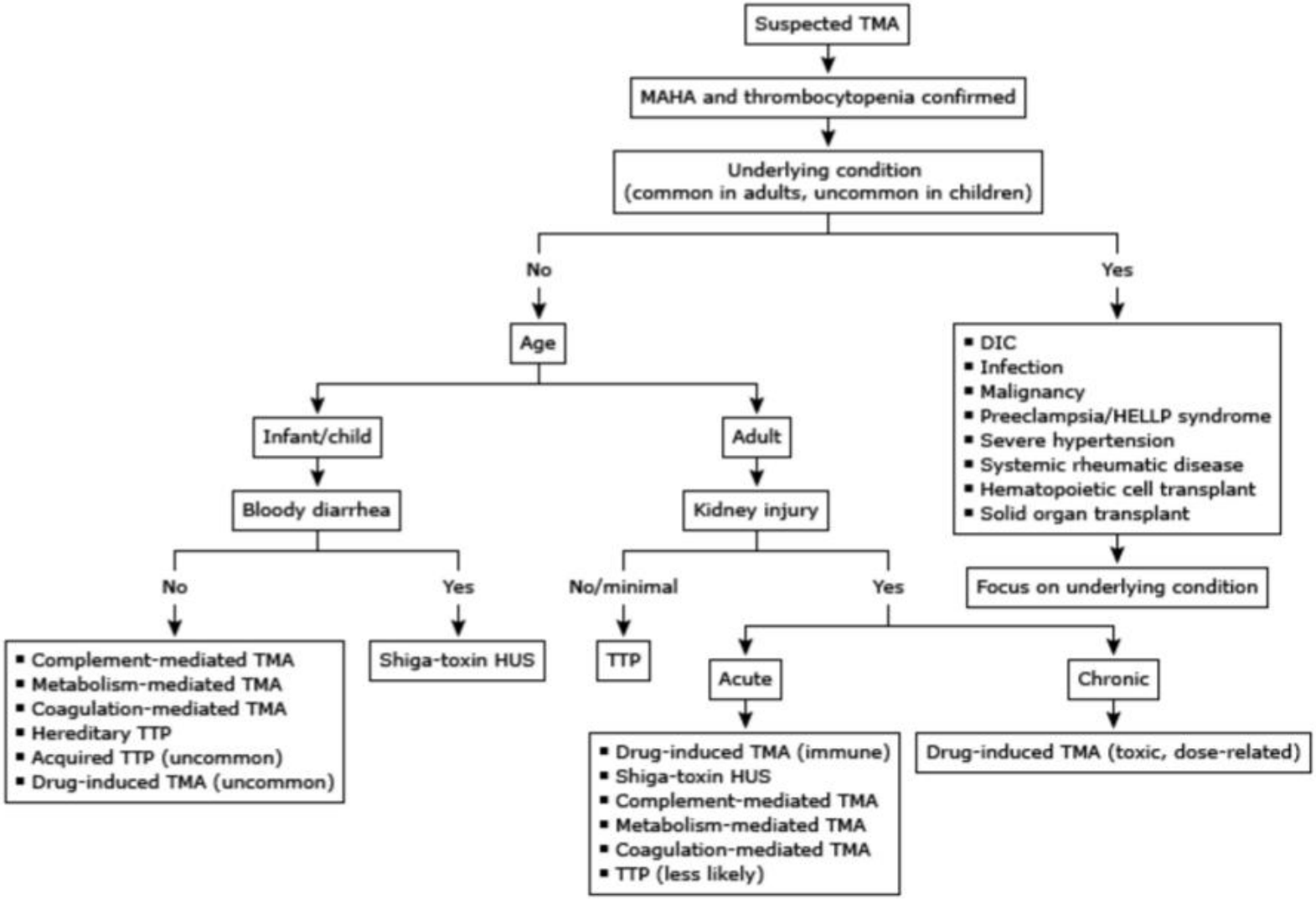
Consiste en la oclusión del lumen del vaso, endoteliosis y aumento de la fibrina, proliferación de la capa media (anillos de cebolla) y formación de coágulos.

Finalmente produciendo daño por hipoxia a órganos blancos con circulación temrinal (riñón, cerebro, retina, miocardio, etc).

Syndromes of Thrombotic Microangiopathy, James N. George, M.D., and Carla M. Nester, M.D. , N Engl J Med 2014;371:654-66.




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


Suspected TMA
MAHA and thrombocytopenia confirmed
Underlying condition
(common in adults, uncommon in children)
No
Yes
Age
DIC
Infection
Malignancy
Preeclampsia/HELLP syndrome
Severe hypertension
Systemic rheumatic disease
Hematopoietic cell transplant
Solid organ transplant
Infant/child
Adult
Bloody diarrhea
Kidney injury
Focus on underlying condition
No
Yes
No/minimal
Yes
Complement-mediated TMA
Metabolism-mediated TMA
Coagulation-mediated TMA
Hereditary TTP
Acquired TTP (uncommon)
Drug-induced TMA (uncommon)
Shiga-toxin HUS
TTP
Acute
Chronic
Drug-induced TMA (immune)
Shiga-toxin HUS
Complement-mediated TMA
Metabolism-mediated TMA
Coagulation-mediated TMA
TTP (less likely)
Drug-induced TMA (toxic, dose-related)

Syndrome	Clinical features	Laboratory findings
Primary thrombotic microangiopathy (TMA) syndromes		
Thrombotic thrombocytopenic purpura (TTP)	May have severe neurologic abnormalities. Inherited; may present in a newborn infant, a child with thrombocytopenia, or, less commonly, an adult. Among adults, a common presentation is during a first pregnancy. Acquired autoimmune: Uncommon in children.	Severe MAHA and thrombocytopenia; acute kidney injury is rare. Severe deficiency of ADAMTS13 (activity <10%). Acquired cases often have a detectable ADAMTS13 inhibitor (autoantibody). Inherited TTP has *ADAMTS13* gene mutation.
Complement-mediated TMA	Inherited and acquired disorders may present in children or adults.	Renal failure is prominent. Inherited disorders usually have a heterozygous mutation in a gene encoding a regulatory protein in the alternate complement pathway (eg, *CFH*, *CFI*, *CD46/MCP*, *C3*, *CFB*, *CFHRs*). Acquired disorder has antibodies to complement factor H or I.
Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)	Abdominal pain; diarrhea (often bloody); possible history of outbreak or exposure to livestock or contaminated food, although most cases are sporadic.	Renal failure is prominent. Stool may be positive for the organism (*Escherichia coli* or *Shigella dysenteriae*) or Shiga toxin.
Drug-induced TMA	History of exposure to quinine or other implicated medication. Immune-mediated forms have an abrupt onset with fever, chills, abdominal pain, nausea, anuric acute kidney injury. Toxic, dose-related etiologies may arise gradually, or onset may be sudden with an intravenous toxic agent (eg, Opana-ER).	Immune mediated: Severe acute kidney injury; drug-dependent antibodies to platelets and/or neutrophils can be demonstrated. Toxic, dose related: May have gradual or sudden onset of renal failure and hypertension.
Coagulation-mediated TMA	Inherited, typically presents in children <1 year old.	*DGKE*, thrombomodulin, or plasminogen gene mutation.
Metabolism-mediated TMA	Inherited, typically presents in children <1 year old, but may also present in adults.	Elevated serum homocysteine and methylmalonic acid, and low methionine levels; increased urinary methyl-malonic acid. *MMACHC* gene mutation.

Systemic disorders that may present with MAHA and thrombocytopenia

Disseminated intravascular coagulation (DIC)	May be caused by infection, malignancy, postpartum hemorrhage with hypotension, or a vascular abnormality such as a giant hemangioma (eg, Kasabach-Merritt syndrome).	Thrombocytopenia, decreased fibrinogen, and elevated D-dimer are typical with acute or chronic DIC. MAHA may occur. Prolongation of the PT and aPTT are seen in acute DIC.
Systemic infection	May include bacterial, viral, rickettsial, or fungal organisms. High fever and shaking chills are common.	
Systemic malignancy	May occur with occult systemic malignancy. Breast, prostate, lung, pancreatic, or gastrointestinal tumors are often responsible.	Depends on specific tumor.
Pregnancy-related syndromes (eg, severe preeclampsia, HELLP)	Typically present in third trimester or postpartum. Severe hypertension and liver involvement are often present. Abnormalities resolve with delivery.	Elevated hepatic transaminases. Acute kidney injury is uncommon.
Severe hypertension	Typically, systolic BP >200 mm Hg and diastolic BP >100 mm Hg. Neurologic features including PRES may be present. Hypertension may also occur in primary TMAs with severe renal involvement, so the temporal relationship is important. Abnormalities resolve with control of the BP.	Often associated with severe renal failure. Renal biopsy demonstrates TMA identical to the primary TMA syndromes.
Systemic rheumatic diseases (eg, SLE, SSc, APS)	SLE may be associated with hypertension, renal insufficiency, and autoimmune cytopenias. APS typically presents with arterial and/or venous thromboembolism but can also produce a TMA.	Serologic testing may show autoantibodies characteristic of the underlying condition; APS may have prolonged aPTT. Renal biopsy may demonstrate TMA identical to the primary TMA syndromes.
Hematopoietic cell transplant	May occur with autologous or allogeneic transplant. May be associated with exposure to cytotoxic chemotherapy, radiation, systemic infection, or a calcineurin inhibitor.	No specific findings.
Solid organ transplant	May be associated with calcineurin inhibitor administration. May be associated with infection such as CMV in the setting of immunosuppression. In patients receiving a kidney transplant for a primary TMA syndrome, the syndrome may recur in the transplanted kidney.	Renal biopsy may have features of rejection.

TRATAMIENTO

HEMODERIVADOS en CASO de EMERGENCIAS

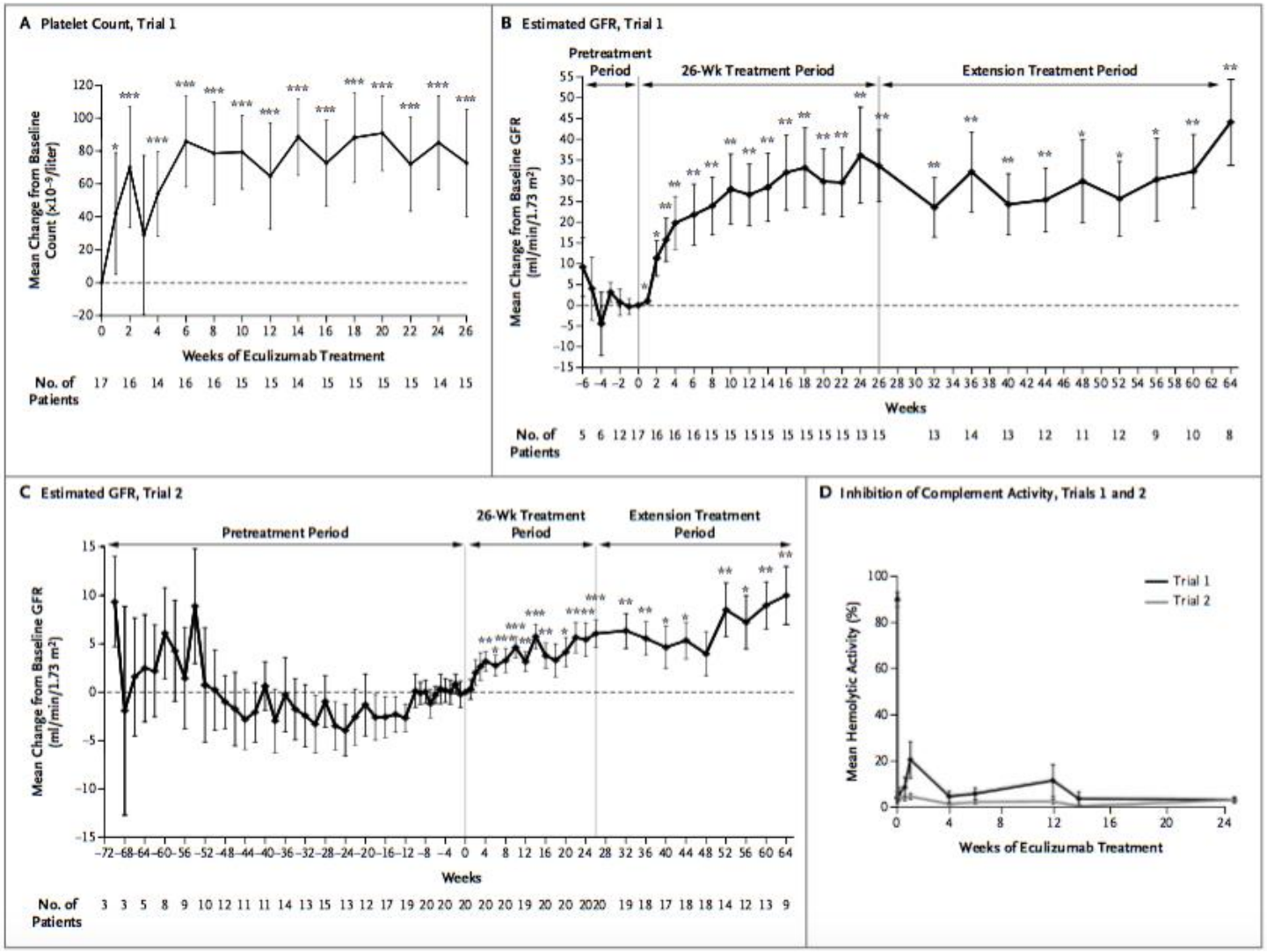
PLASMA FRESCO CONGELADO

PLASMAFERESIS *(1° indicación PTT, resto de etiologías considerar opción)*

Complicaciones: reacciones alérgicas con hipoxemia, hipotensión y enfermedad del suero; asociadas al uso de catéter venoso central como bacteremia, obstrucción del catéter, hemorragia, fungemia, trombosis venosa, neumotorax. Otras complicaciones son urticaria, infección local del sitio de inserción del catéter, toxicidad por citrato

CORTICOIDES

ECULIZUMAB *(en AMAT mediada por complemento)*



Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome, N Engl J Med 2013;368:2169-81.

CONCLUSIONES

Patología de baja frecuente pero de **ALTA MORTALIDAD**

Se debe **SOSPECHAR** en:

- **Anemia moderada aguda/subaguda** *(no inmune = Test Coombs directo -)*
- **LDH elevada**
- **Esquistocitos (> 1%)**

La sospecha diagnóstica BASTA para iniciar TERAPIA

- Ideal tomar muestra de sangra para estudio de ADAMTS13

El **recambio plasmático terapéutico con PFC es la terapia de primera línea**.

GRACIAS