Policlinico Agostino Gemelli
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# Aspetti clinici delle microangiopatie trombotiche

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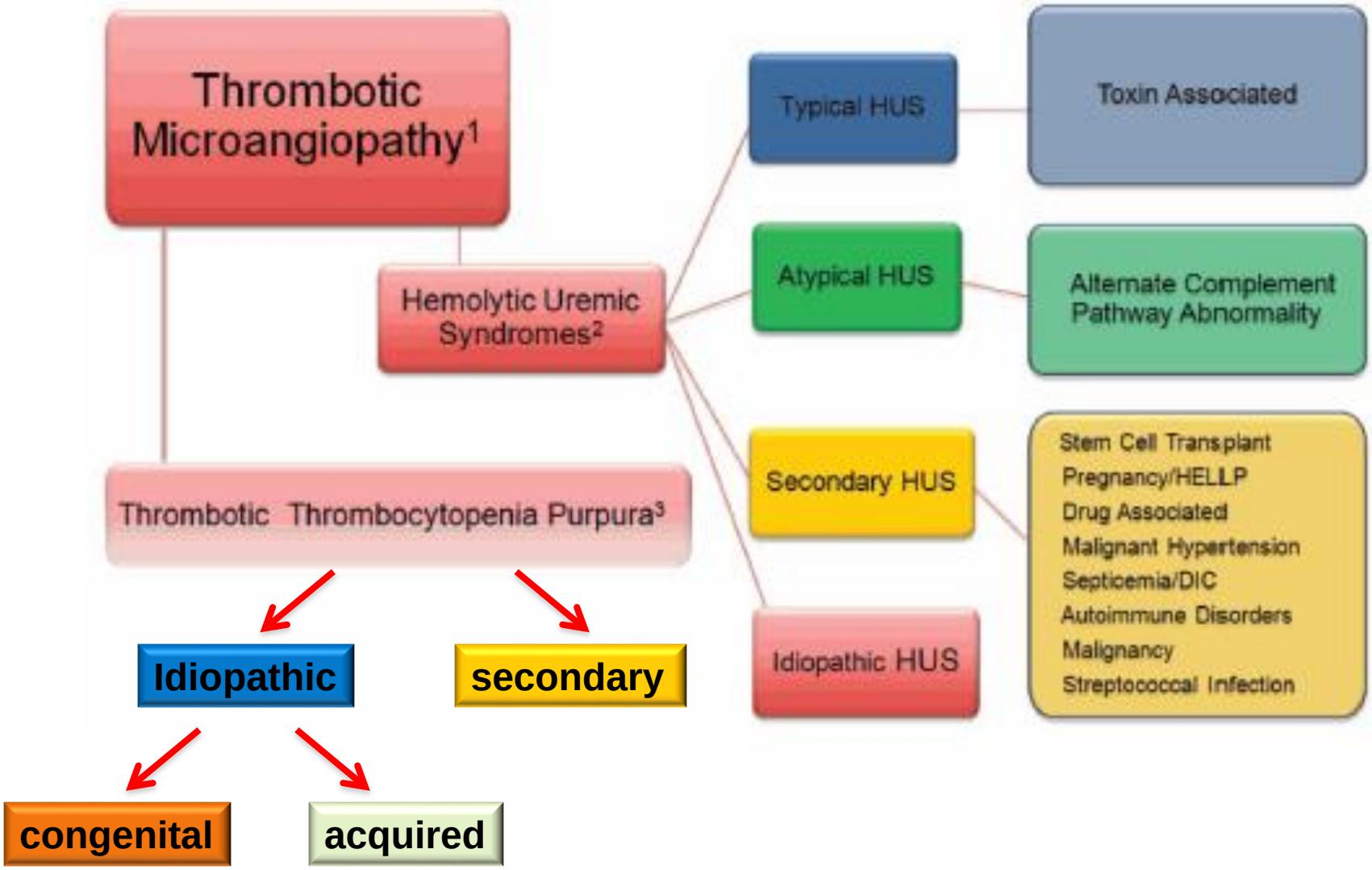
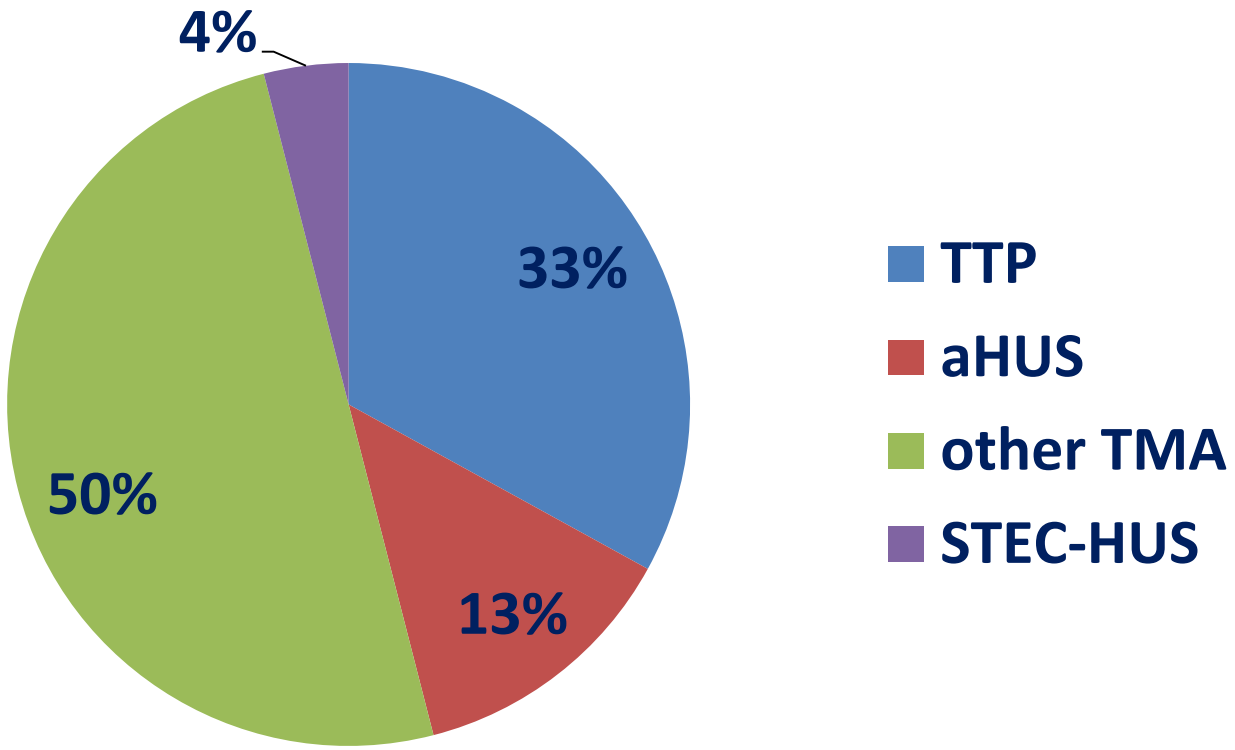
**Roma**

# La famiglia delle Microangiopatie Trombotiche TMA



# Incidenza delle TMA nel 2014
## (Registro delle TMA Del Johns Hopkins)




*Sperati e Molitieno, Hematol Oncol Clin North Am. 2015*

# TTP - Thrombotic Thrombocytopenic Purpura

**A process, characterized by abnormal activation of platelets and endothelial cells, with fibrin deposition in the microvasculature, and peripheral destruction of platelets and red cells**

# AN ACUTE FEBRILE PLEIOCHROMIC ANEMIA WITH HYALINE THROMBOSIS OF THE TERMINAL ARTERIOLES AND CAPILLARIES

### AN UNDESCRIBED DISEASE*


## ELI MOSCHCOWITZ, M.D.
NEW YORK

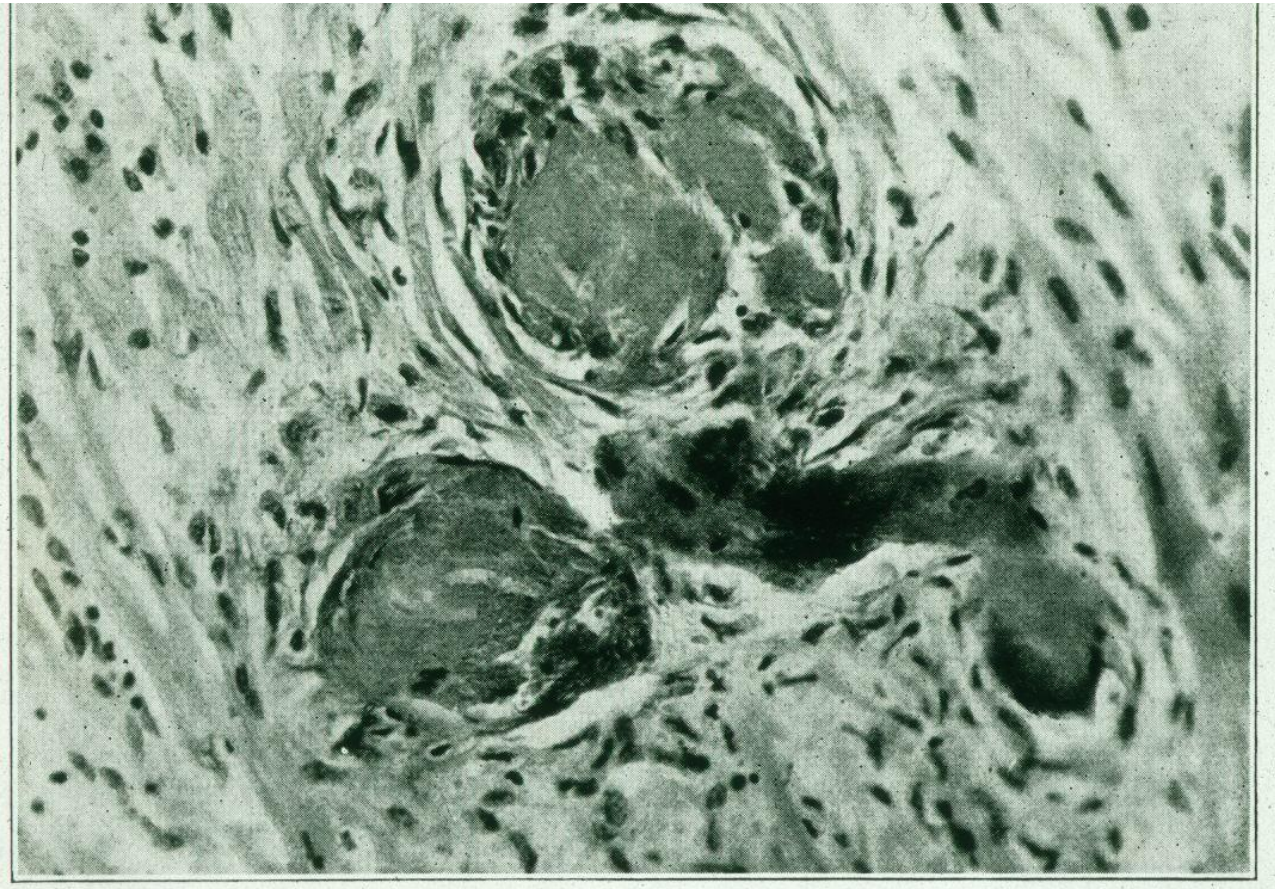

This case is remarkable, clinically and anatomically.

### REPORT OF CASE

***History***-K.Z., a girl, aged 16 years, was an elementary school graduate, had gone to business school, and had been employed for eight months preceding the illness. There were three other children, two younger and one older; all apparently were perfectly normal. There were no home difficulties, and poverty was not extreme. She had spent September 4 and 5 at Rockaway Beach, where she appeared in perfect health and spirits. She had returned home on the evening of September 5 and slept well. On the morning of September 6, she complained of weakness in the upper extremities and had pain on moving the wrist and elbows; she already had marked pallor and was slightly constipated. The symptoms increased in severity until she was admitted to the Beth Israel Hospital, September 15. While at home, she had a constant fever, the temperature rising once to 104 F, and staying at other times between 101 and 102 F.


***Arch Int Med 36:89, 1925***


**a 16 yo girl with abrupt onset of petechiae, pallor, followed by paralysis, coma, and death.**



-Section of heart muscle, showing hyaline thrombi with beginning organization.

Moschcowitz, Arch. Int. Med., 36:89, 1925

**Autopsy showed ‘hyaline’ thrombi occluding terminal arterioles and capillaries**

# PTT congenita
# Upshaw-Schulman Syndrome

*(NEJM 1978;298:1350)*

- Pazienti affetti sono doppi eterozigoti o portatori omozigoti di alleli mutati per ADAMTS-13. Gli eterozigoti sono asintomatici
- Più di 140 mutazioni (60% missense)
- Al momento non c' è correlazione tra genotipo e fenotipo di malattia
- Circa la metà dei pazienti ha il loro primo episodio entro il 5° anno di vita; l' altra metà tra i 20 e i 40 anni e c' è anche qualcuno che non sviluppa ancora la malattia
- Probabilmente tre fattori contribuiscono alla variabilità clinica: la mutazione di ADAMTS, altri geni che possono modificare la malattia, fattori ambientali (febbre, diarrea, gravidanze , chirurgia)
- Frequenti le recidive
- Rara la malattia, difficile la diagnosi; spesso è soltanto autoptica.
- Misdiagnosticata nei bambini (atipiche porpore immunologiche o sindrome di Evans con il Coombs negativo)

# Clinica

- Anemia emolitica microangiopatica con **iperbilirubinemia**
  - **Trombocitopenia tipicamente entro poche ore dalla nascita**
  - **Occasionalmente può essere complicata da pancreatite, deficit neurologici focali, convulsioni, lieve insufficienza renale, microematuria**
- Trattamento e Prognosi:
  - Plasma 20-40 ml/kg ogni 2-4 sett, o meno spesso
  - ADAMTS-13 t/2 è 3-4 giorni
  - 5% di ADAMTS13 previene le manifestazioni cliniche

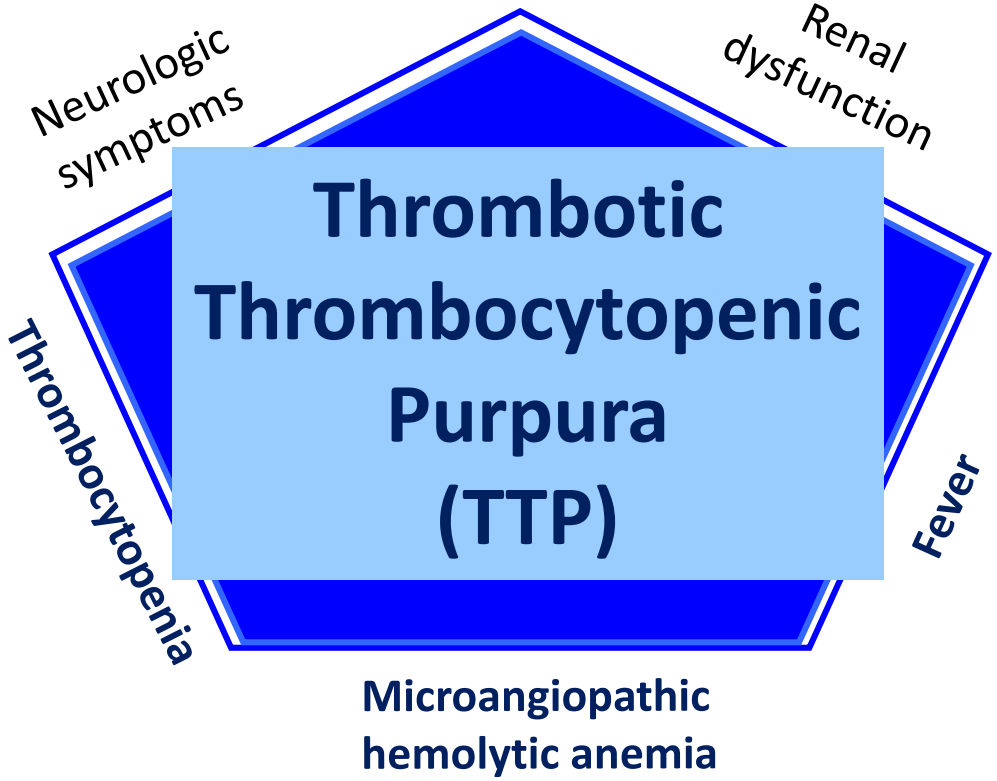
# PTT acquisita

- Rara: 4-6 casi/ milione
- Femmine: 70% dei casi.
- Picco incidenza: 4. decade
- Acuta, emergenza, pericolo di vita
- >70% casi idiopatica
- Anticorpi anti-ADAMTS nel 90% delle forme acquisite.
- IgG soprattutto, descritti casi IgM/IgA.
- spesso anticorpo inibitore

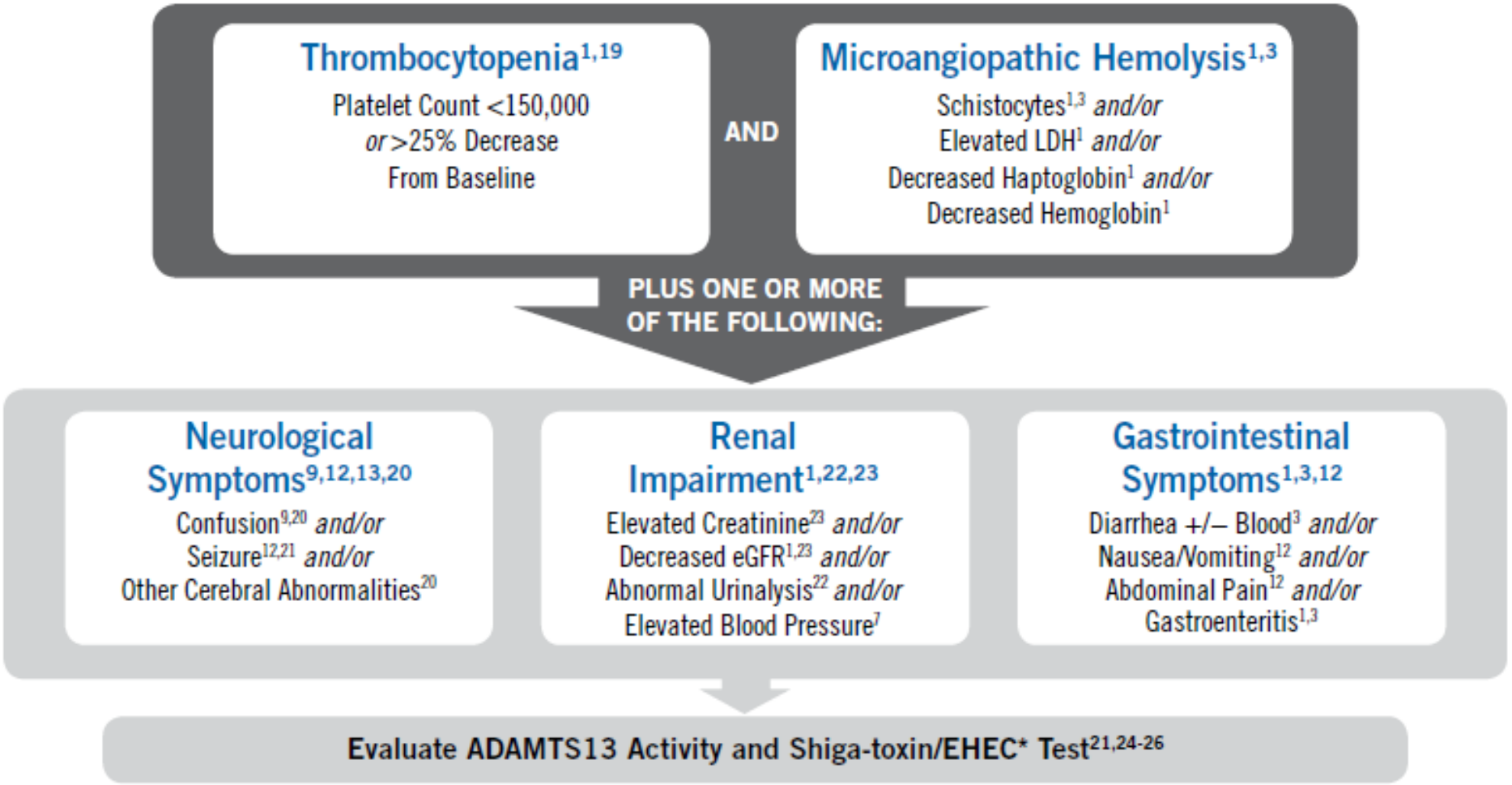
**Dosaggio ADAMTS-13**

| ADAMTS13 deficiency | ADAMTS13 Inhibitor |
|---|---|
| 34% to 100% | 50% to 100% |

# La Pentade



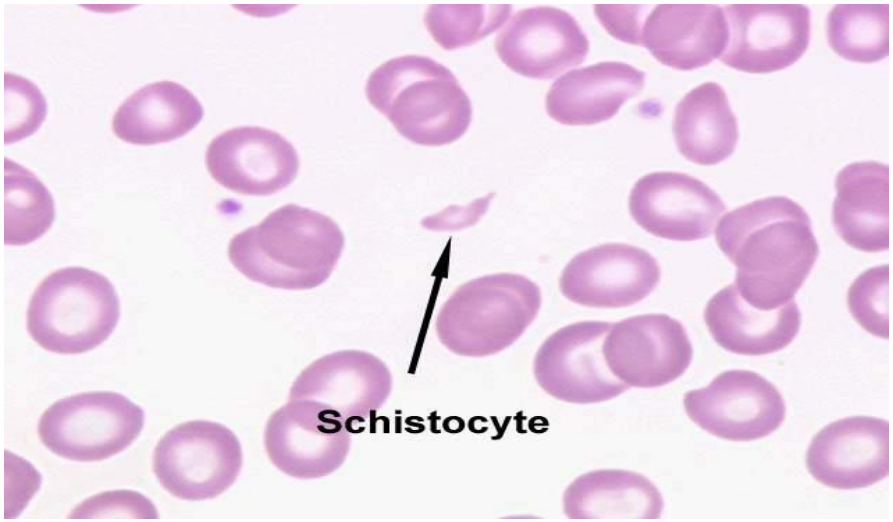

- Moscowitz Syndrome (1924)

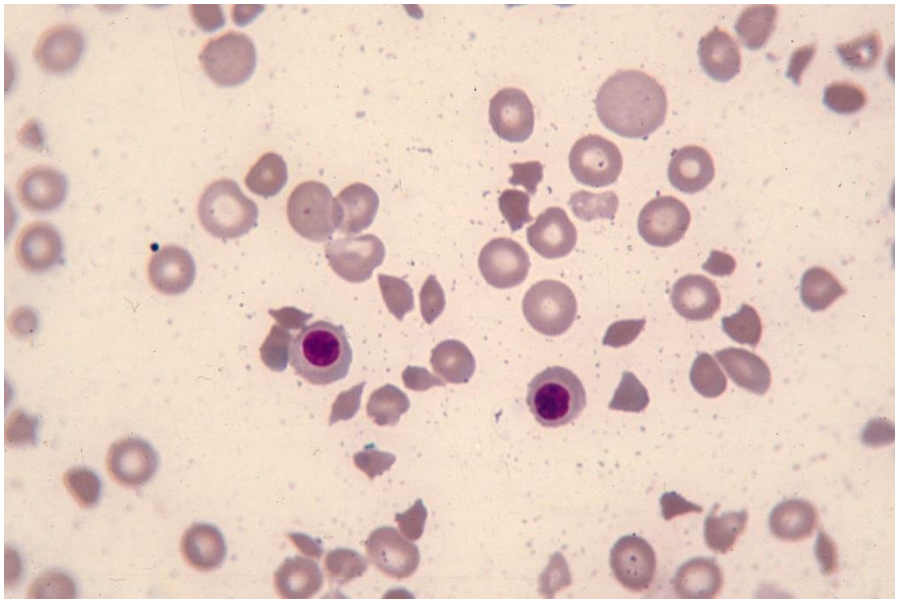



Laurence J. *Clin Adv Hematol Oncol. 2012 Oct;10:1-12.*

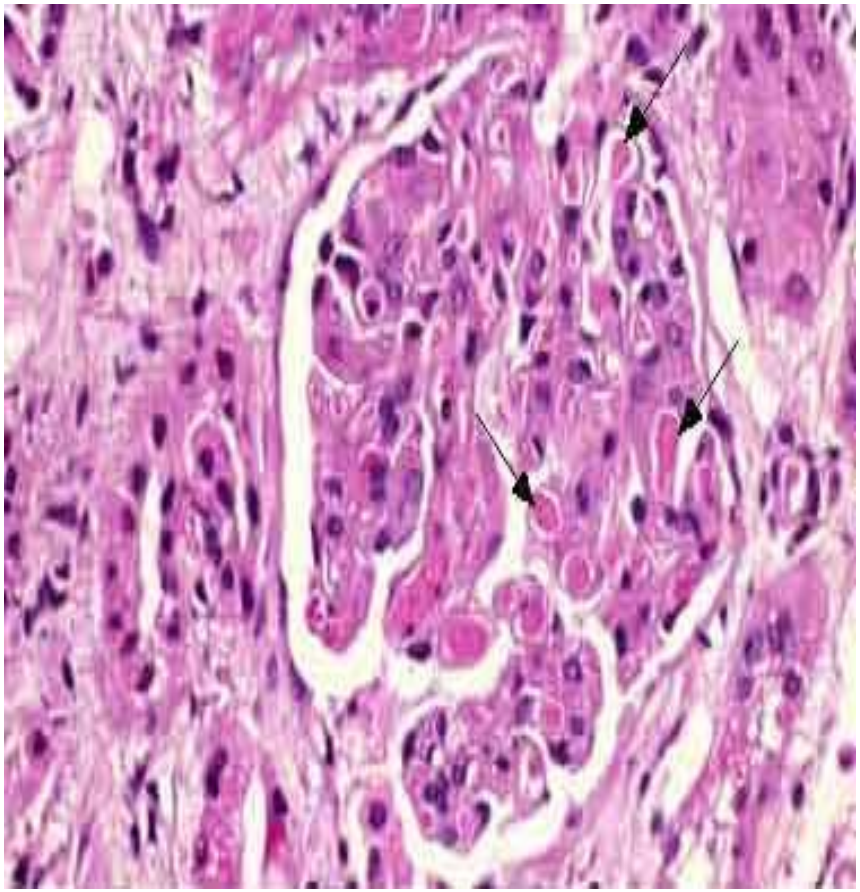
# Anemia Emolitica Microangiopatica
## (MAHA)

**L'anemia emolitica microangiopatica è un'emolisi meccanica , da frammentazione delle emazie, causata da un danno in circolo della membrana eritrocitaria, con conseguente emolisi intravascolare e comparsa di schistociti nello striscio periferico**



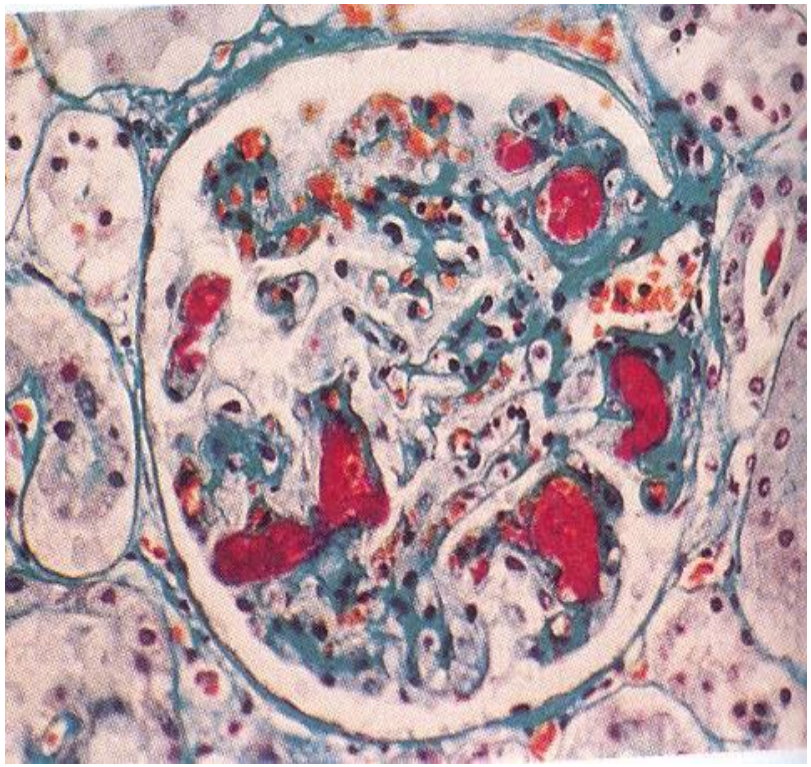



# Microangiopatia Trombotica (TMA)



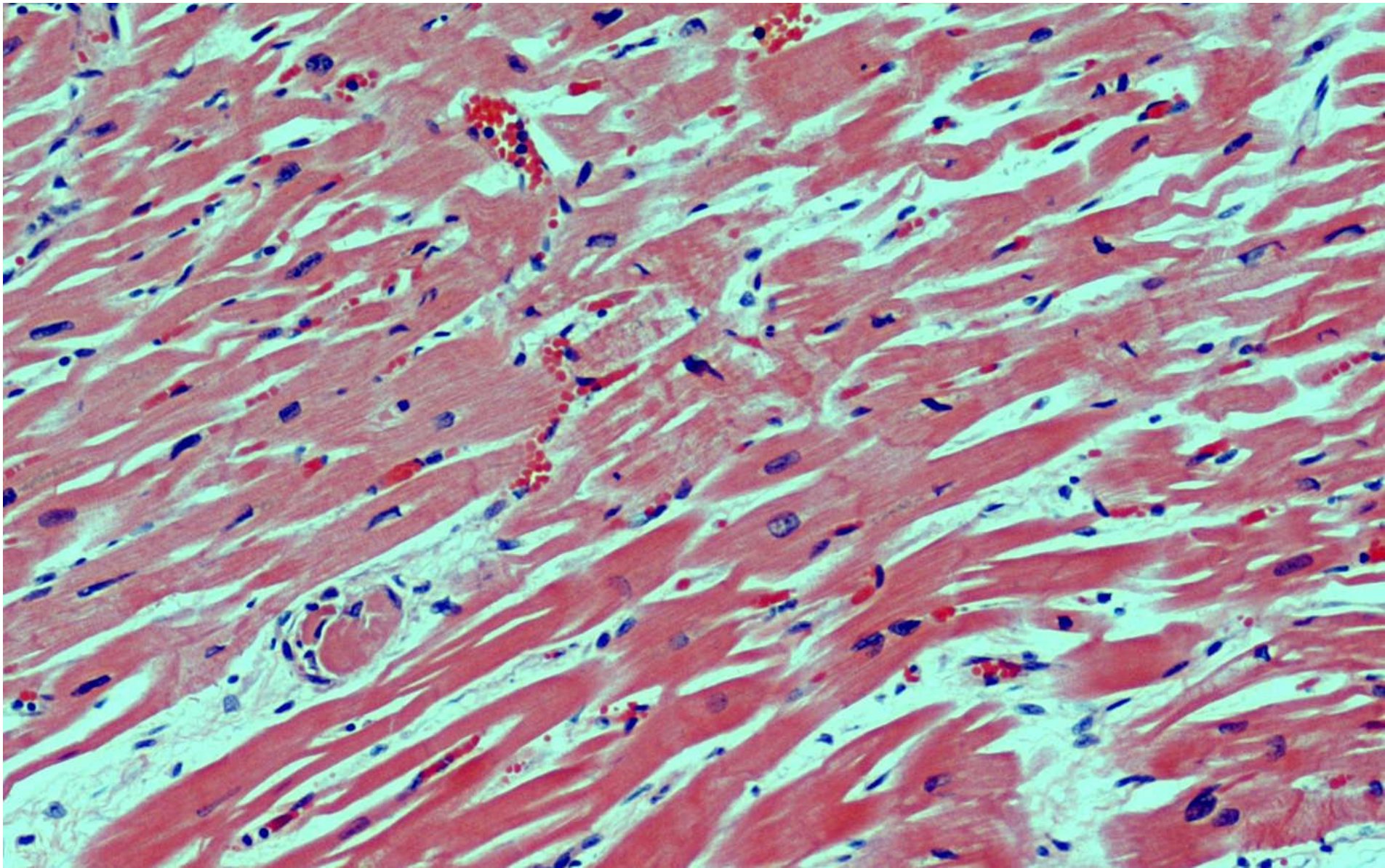
Fibrin stain.

Platelet-fibrin thrombi (red) in glomerular capillaries.

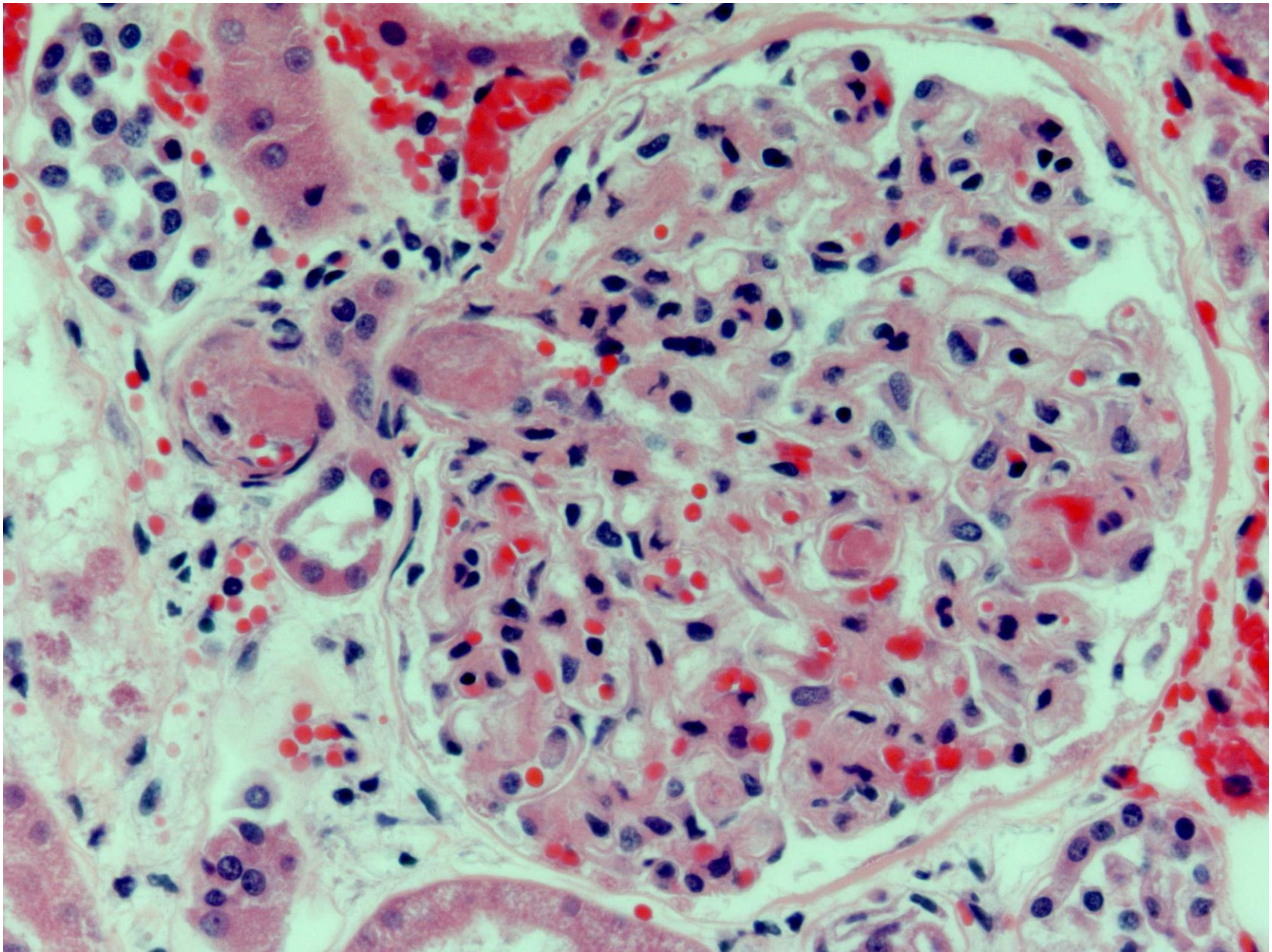


**Istologicamente:**
**si tratta di trombi ialini nelle zone terminali delle arteriole e dei capillari con infiltrazioni di tessuto fibroblastico.**
**Reperti autoptici: cervello, rene, cuore, pancreassurreni, milza..**

# TTP.Heart



# TTP.Kidney



# Diagnostic and therapeutic challenges in the thrombotic thrombocytopenic purpura and hemolytic uremic syndromes

*James N. George[1] and Zayd L. Al-Nouri[1]*

*[1]Department of Biostatistics and Epidemiology, College of Public Health, Department of Medicine, College of Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, OK*

**Table 3. Presenting clinical features of 70 consecutive patients with severe ADAMTS13 deficiency (activity < 10%)**

| Clinical feature | Frequency |
|---|---|
| Thrombocytopenia | 70 (100%) |
| Microangiopathic hemolytic anemia | 70 (100%) |
| **Neurologic abnormalities** | |
| Severe | 25 (36%) |
| Minimal | 21 (30%) |
| None | 24 (34%) |
| **Kidney function abnormalities** | |
| Acute renal failure | 6 (9%) |
| Renal insufficiency | 29 (41%) |
| None (normal renal function) | 35 (50%) |
| Fever | 15 (21%) |
| Complete pentad of clinical features | 3 (4%) |

**Table 2. Frequency of severe ADAMTS13 deficiency (activity < 10%) among patients for whom PEX treatment was requested for an initial clinical diagnosis of TTP or HUS: the Oklahoma TTP-HUS Registry experience, 1995-2011**

| Clinical category | Frequency of patients with ADAMTS13 < 10% |
|---|---|
| Stem cell transplantation | 1/12 (8%) |
| Pregnancy | 3/17 (18%) |
| Drug associated | 0/39 |
| Bloody diarrhea prodrome | 2/30 (7%) |
| **Additional or alternative disorder** | |
| Autoimmune disorders | 4/40 (10%) |
| Sepsis | 4/25 (16%) |
| Systemic malignancy | 1/10 (10%) |
| Other disorders | 0/19 |
| Idiopathic | 55/119 (46%) |

From November 13, 1995 through December 31, 2011, 301 (93%) of 333 consecutive patients enrolled in the Registry had ADAMTS13 activity measured in a sample obtained immediately before beginning the initial PEX by both FRETS and immunoblotting assays.[3]

# TTP: Evolution of the Syndromes

| | 1925-1964 | 1964-1980 | 1982-1989 |
|---|---|---|---|
| Thrombocytopenia | 96% | 96% | 100% |
| Hemolytic anemia | 96% | 98% | 100% |
| Neurologic symptoms | 92% | 84% | 63% |
| Renal failure | 88% | 76% | 59% |
| Fever | 98% | 59% | 26% |
| Survival | 10% | 46% | 78% |

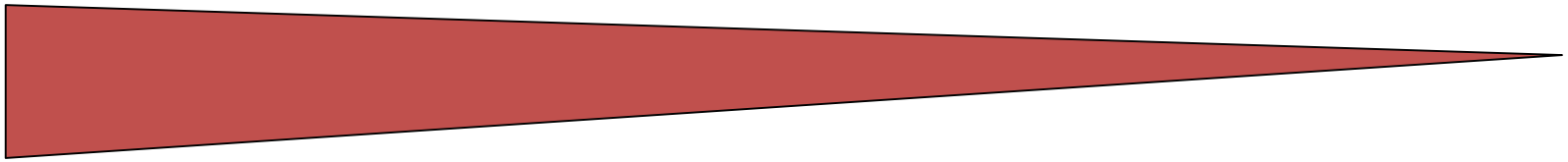
# HUS - Hemolytic Uremic Syndrome

- Usually classified along with TTP as "TTP/HUS"
- Has fewer neurologic sequelae, more renal manifestations
- Usually precipitated by diarrheal illness, especially E. coli O157:H7 or Shigella
- Seen more in pediatric patients, usually has better prognosis. May respond less well to plasma exchange.

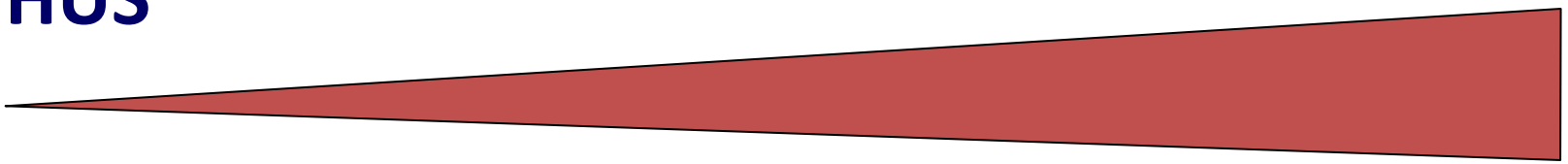
# PTT e HUS

**CNS  febbre  MAHA  piastrinopenia  insufficienza renale**

**TTP**



**HUS**



# S.Emolitica-Uremica (HUS) tipica

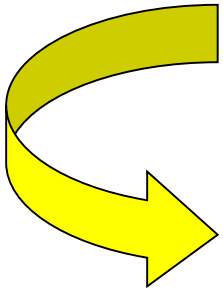
**La forma più tipica del bambino**

- **Insufficienza renale acuta**
- **Trombocitopenia**
- **Anemia emolitica microangiopatica**
- **Preceduta tipicamente da diarrea**

***Agente più frequentemente implicato***

***E.Coli 0157:H7. (90%)***

- La HUS post-diarrea negli in USA e' dovuta a EHEC nel 70% dei casi.
- EHEC causa il 9% delle HUS



**Patogenesi:**

**Produzione di ShigaToxin (STEC o EHEC)**

**Colonizza parte dell' intestino (aderisce alle cellule epiteliali)**

**La tossina Shiga si lega al recettore glicolipidico (Gb3) (preferenzialmente espresso nelle cellule endoteliali renali e glomerulari)**

**Distretti più interessati: rene cervello**

# Presentazione alla diagnosi

**Table 2. Presentation of aHUS from the largest European cohort[4]**

| | | |
|---|---|---|
| Pediatric (<18 y) | 152 | 59% |
| Adult (>18 y; n = 256) | 104 | 41% |
| Male/female (n = 245) | 125/120 | 51%/49% |
| **Trigger/associated finding (n = 191)** | | |
| Diarrhea | 45 | 24% |
| Respiratory infection | 35 | 18% |
| Pregnancy | 13 | 7%-20%[2] |
| Secondary HUS | 30 | 16% |
| **Extrarenal manifestations (n = 211)** | | |
| Multiorgan | 12 | 6% |
| Cardiovascular only | 7 | 3% |
| CNS only | 23 | 11% |

## Spesso sintomi aspecifici

- Anuria, oligoanuria
- Ipertensione arteriosa
- Danni neurologici: irritabilità, crisi convulsive, diplopia, emiparesi, emiplegia, stupor , coma
- IMA
- MOF

**3-5% di mortalità**

# Microangiopatia post-TMO (TMA)

## DEFINIZIONE:

sindrome clinica caratterizzata da ostruzione del microcircolo periferico (piccole arteriole, piccoli capillari) con microtrombi dovuti ad aggregati piastrinici e contemporanea proliferazione di cellule endoteliali. Più frequente nell ´ alloBMT che nell´ autoBMT.

•**SEDI**:

•rene, fegato, polmone, sistema nervoso centrale

•**SINTOMI**:

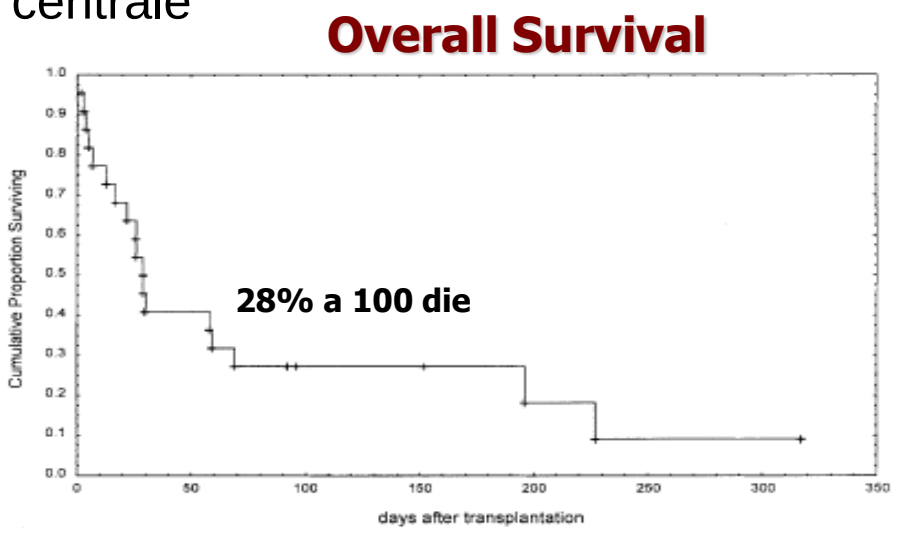
•• **anemia emolitica microangiopatica**

•• **diatesi emorragica**

•• **coinvolgimento SNC**

•• **insufficienza renale**

•• **febbre**




•**MORTALITÀ**: