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TTP e aHUS: la terapia

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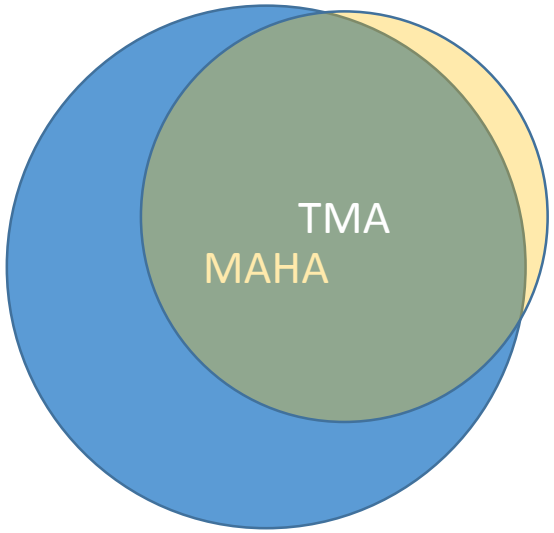
Definitions

- Thrombotic microangiopathy (TMA) is a specific pathologic lesion characterized by microvascular thrombosis (arterioles and capillaries)
- It is commonly inferred from the observation of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia
- Not all MAHA are caused by TMA, but TMA is usually associated with MAHA



TMA: Clinical subtypes

- Thrombotic thrombocytopenic purpura (TTP)
  - Congenital TTP (Upshaw-Shulman syndrome)
  - Acquired TTP (Moskowitz syndrome)
- Complement-mediated (Atypical) HUS
  - Complement gene mutations
  - Antibodies to complement factor H (CFH)
- Shiga-toxin (STEC) HUS
- Drug induced
  - Immune-mediated (Quinine, gemcitabine)
  - Toxicity-mediated (e.g., Cyclosporine, tacrolimus, gemcitabine)
- Vitamin B12 deficiency (*MMACHC* gene [MethylMalonic ACiduria and Homocystinuria type C] defect)
- Systemic disorders (CAPS, HELLP, HIV, Malignancy, Malignant Hypertension, HCT)

Conditions mimicking TTP

Disorder	Comments
Preeclampsia, HELLP syndrome	Can cause microangiopathic hemolytic anemia, thrombocytopenia, renal failure, and minor neurologic abnormalities. May first present after delivery. TTP diagnosed if major neurologic abnormalities occur or if abnormalities fail to resolve within 3 days after delivery.[27]
Autoimmune disorders	May be indistinguishable from TTP. Some patients may have both TTP and an additional autoimmune disorder, such as SLE or APLA.[36]
Systemic infection	Multiple etiologies of sepsis (bacteria, fungi, rickettsiae, and viruses) can cause thrombocytopenia and microangiopathic hemolytic anemia without signs of DIC.[37] Sepsis suggested by high fever with chills and pulmonary infiltrates, which rarely if ever occur in TTP.
Systemic malignancy	Multiple malignancies can cause thrombocytopenia and microangiopathic hemolytic anemia without signs of DIC. Malignancy suggested by hepatic and pulmonary involvement, which rarely if ever occur in TTP.[10] Nucleated red cells and immature white cells on the peripheral blood smear suggest marrow involvement that may be diagnosed by marrow biopsy.[38,39]
Malignant hypertension	Can cause thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and severe neurologic abnormalities.[45]

George Blood, 2010.

Hereditary TTP
(Upshaw-Schulman syndrome)

- Similar to TTP, but more frequent in pregnancy & childhood
- Autosomal recessive
- Misdiagnosis frequent (ITP, Alloimmune thrombocytopenia, HELLP)
- ADAMTS13↓↓, Inhib –

Hereditary TTP - Treatment
(Upshaw-Schulman syndrome)

- PEX not required
- FFP 10-15 ml/kg for three days, then
- FFP 10-15 ml/kg every 3-4 days, until resolution

Hereditary TTP - Prophylaxis
(Upshaw-Schulman syndrome)

- Many patients may experience fatigue, or headaches
- Prophylactic plasma infusion may improve those symptoms
- Prophylaxis is also required
  - Before/after surgery
  - Infections
  - Pregnancy (until six weeks post-partum)

- Usual dose: FFP 10-15 ml/kg every two weeks
- rADAMTS-13 under development

Acquired TTP: Initial treatment

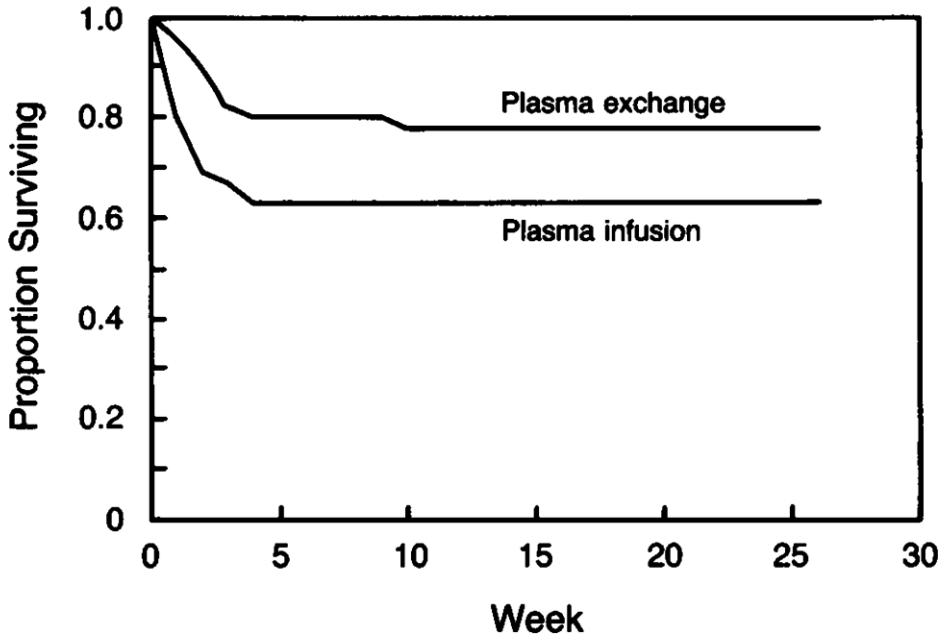


Figure 1. Survival of Patients with Thrombotic Thrombocytopenic Purpura.
The survival curves differ significantly (P = 0.036 by the Breslow–Gehan test).

Rock et al. N Engl J Med, 1991.

Acquired TTP: Initial treatment

- PEX should be initiated as soon as possible
- Glucorticoids (prednisone 1 mg/Kg bw/day) are a possible added measure
- Maintain PEX for at least 2 additional procedures after Plt>150 000/µl

- HIV-related: PEX+HAART
- Cancer-related: PEX not effective

Scully et al. British Journal of Haematology, 2012.

Plasma Exchange

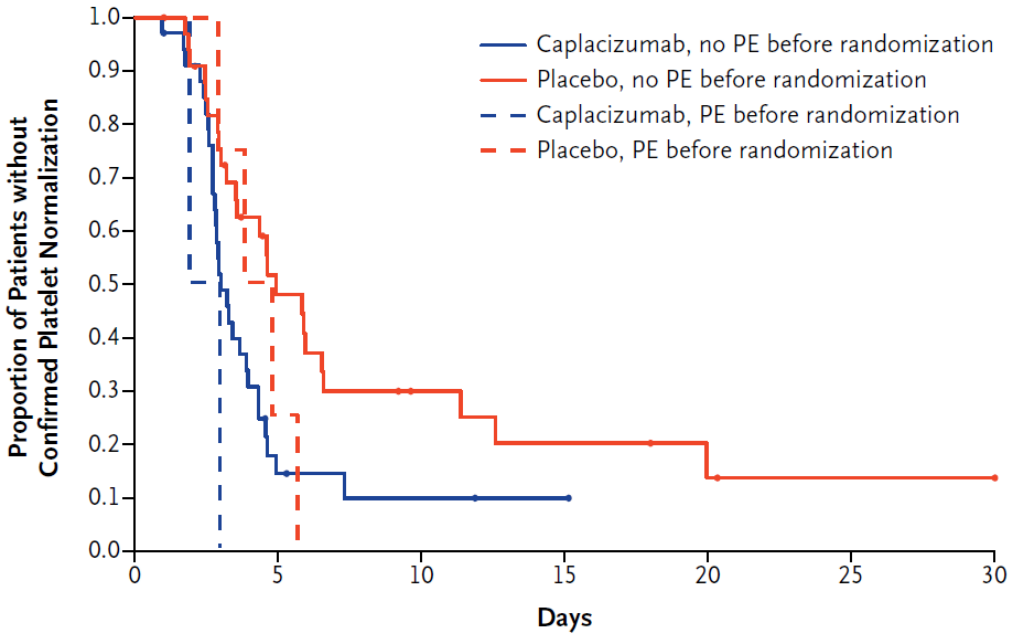
- Bilumen CVC needed
- FFP or CryoPoor Plasma (monitor for FVIII/Fibrinogen content after procedure)
- 40 ml/kg volume per day
- Plasma 10-15 ml/kg may be given if estimated time to PEX>6 hrs

- Side/Adverse effects
  - TRALI, ion/clotting inbalance

Scully et al. British Journal of Haematology, 2012.

Acquired TTP: AntiVWF (caplacizumab)

- A humanized monoclonal antibody based fragment (a nanobody) that binds to VWF and blocks VWF interaction with platelet GPIb-IX-V.
- Associated with a two-day reduction in the time to complete response when associated with PEX
- More bleeding-related adverse events (54% vs. 38%)



Peyvandi et al. New England Journal of Medicine, 2016.

Acquired TTP: additional measures

- ASA: unproven efficacy to prevent vascular complications
- Add Folate if hemolysis
- Thromboprophylaxis with LMWH is recommended once platelet count >50.000/ul
- Platelet transfusions are contra-indicated in TTP unless there is life-threatening hemorrhage
- RBC support

Scully et al. British Journal of Haematology, 2012.

TTP remission

- Normalization of platelet count and absence of TTP symptoms for 30 days after PEX is stopped

TTP relapse

- Recurrence of an acute episode, manifested by thrombocytopenia and microangiopathic hemolytic anemia, in a patient who had a disease remission following an episode of TTP

TTP Relapse

- ≈ 10-15% early relapses: keep CVC for 7-10 days after remission has been achieved
- ≈ 20-25% late relapses: follow-up for at least one year with scheduled visits

Treatment of relapsed TTP

First-relapse

- PEX+Prednisone 1 mg/kg
- Cyclophosphamide
- Cyclosporine, 2-3 mg/kg daily in twice daily divided doses

- Some data suggesting that Rituximab may prevent relapsing TTP

Page et al. Blood, 2016.

Refractory TTP

- Failure of the platelet count to double after four days
- New neurologic abnormalities during PEX
- Exacerbation of symptoms or laboratory findings occurs during PEX or within the first 30 days of stopping PEX

Treatment of refractory TTP

≈10% patients do not respond; ≈25% patients have early relapse after PEX suspension

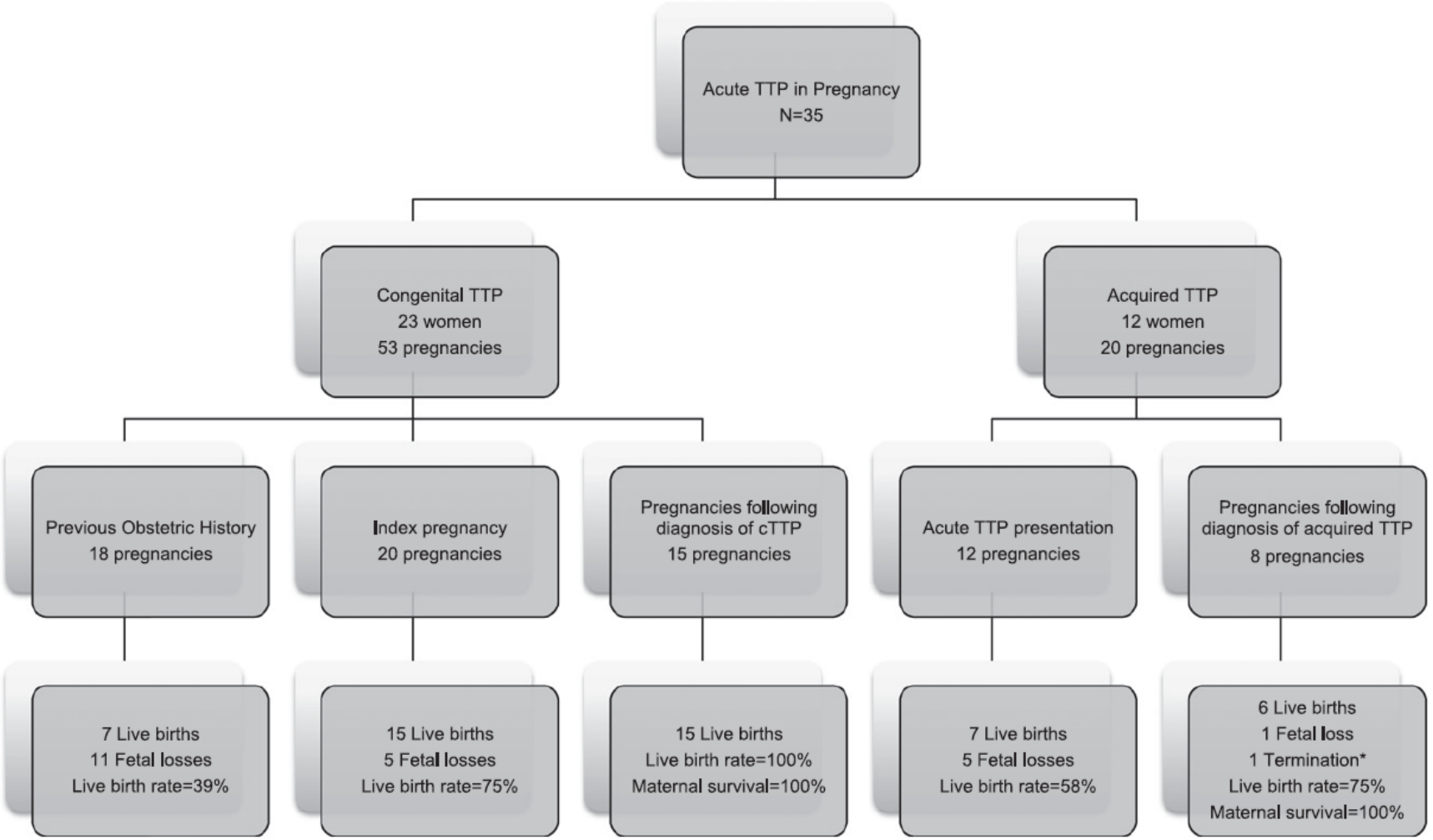
- Search for secondary causes of TTP (e.g., cancer)
- Re-evaluate ADAMTS13 levels/inhibitors
- Restart PEX if suspended
- HD steroids (e.g., methylprednisolone 1 g for 3 days)
- Rituximab, 375 mg/m^2 i.v. once a week for four consecutive weeks immediately after PEX

Treatment of refractory TTP

“Third-line” therapies after rituximab failure

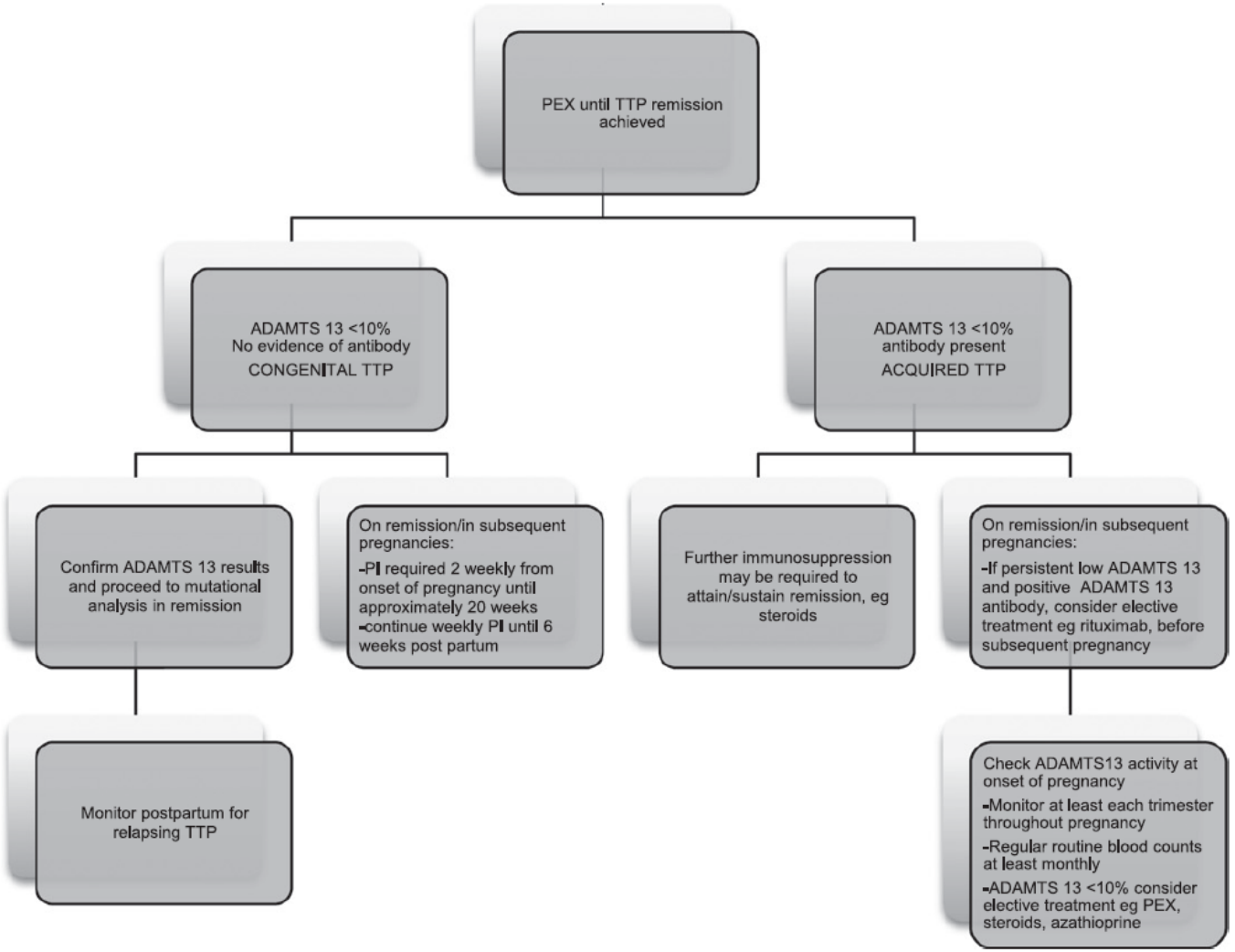
- Prednisone 1 mg/kg and rituximab may be continued
- Cyclophosphamide
- Bortezomib, 1.3 mg/m^2 s.c. twice weekly for two weeks
- Cyclosporine, 2-3 mg/kg daily in twice daily divided doses
- Mycophenolate mofetil, 250-750 mg orally b.i.d.
- Splenectomy

TTP in pregnancy – the UK experience



Scully et al. Blood, 2014.

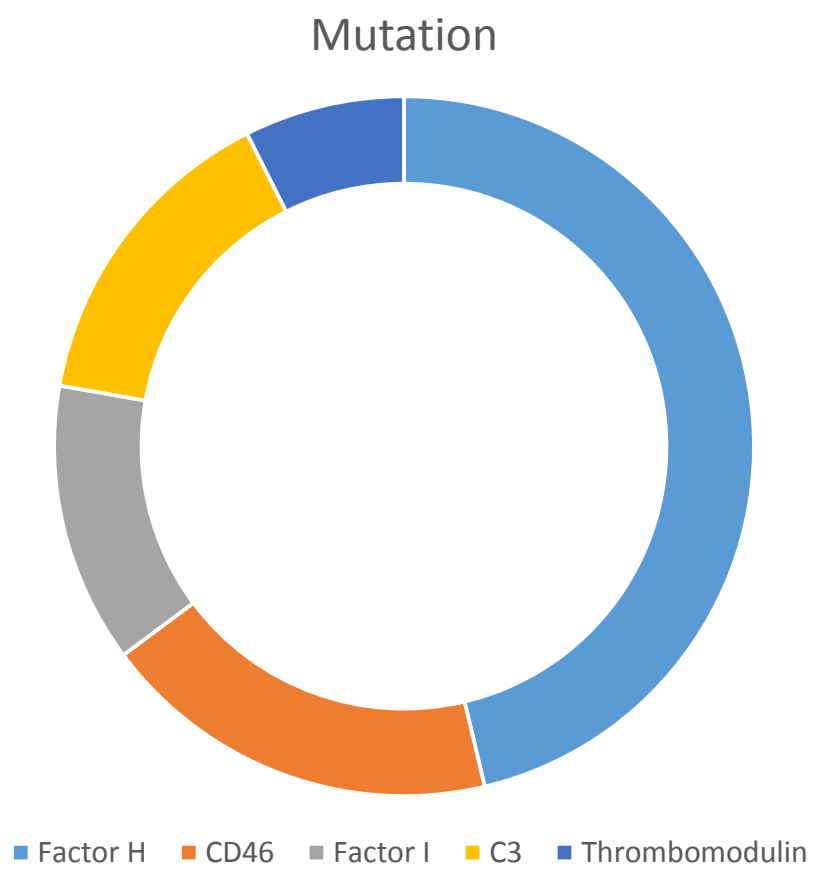
TTP in pregnancy – the UK experience



Scully et al. Blood, 2014.

Complement-mediated HUS

- Mutations account for ≈ 50-60% of STEC-HUS
  - Multiple mutations detected in the same patient
  - Penetrance low, <50% affected family members ever symptomatic
  - Unknown trigger events?
- Complement antibodies
  - Reported in ≈ 10% patients
  - Factor H



Complement-mediated HUS

- Half of the cases are pediatric
- History of hypertension, kidney disease, or previous HUS
- Triad of MAHA, thrombocytopenia, and acute kidney injury

Exclude TTP/STEC-HUS:

- Shiga toxins (eg, stool ELISA), stool cultures for Shiga E. Coli
- ADAMTS13>10%

Support complement-mediated HUS

- ↑C5a
- ↑C5b-9

C5a and C5b-9 are sensitive (but aspecific) markers to differentiate aHUS from TTP

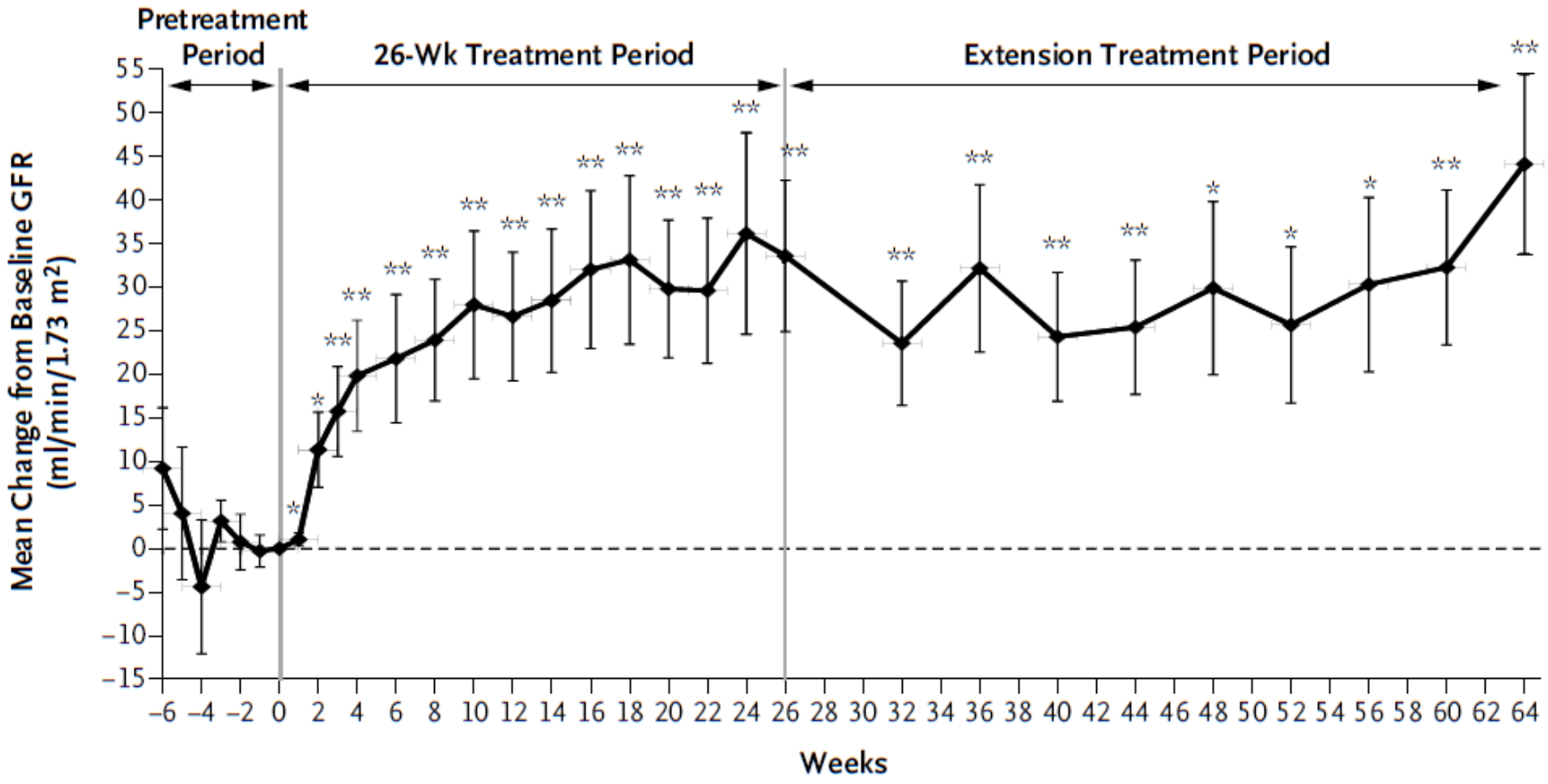
	Complement biomarkers (ng/mL)				
Clinical diagnosis	**Factor Bb (244.3-960.8)**	**C4d (278.5-1845.9)**	**C5b-9 (33.9-238.2)**	**C5a (18.6-47.9)**	**C3a (6.9-242.3)**
Acquired TTP*[6] (n = 38)	2153 (343-5448)	3534 (458-7450)	585 (210-1924)	75 (29-210)	777 (128-4782)
aHUS* (n = 19)	7386 (603-30 610)	2914 (1394-15 210)	1098 (422-4840)	115 (55-280)	1237 (79-13 730)
P value†	.063	.706	**< .0001**	**.004**	**.031**

Cataland et al. Blood, 2014.

Complement-mediated HUS: Treatment

- PEX could be considered only if kidney function is not deteriorating, or neurologic symptoms
- Eculizumab: first-line treatment
- Supportive care
  - RBC transfusions
  - Appropriate fluid and electrolyte management; adequate nutrition
  - Stopping nephrotoxic drugs
  - Initiation of dialysis therapy

Eculizumab in aHUS: GFR



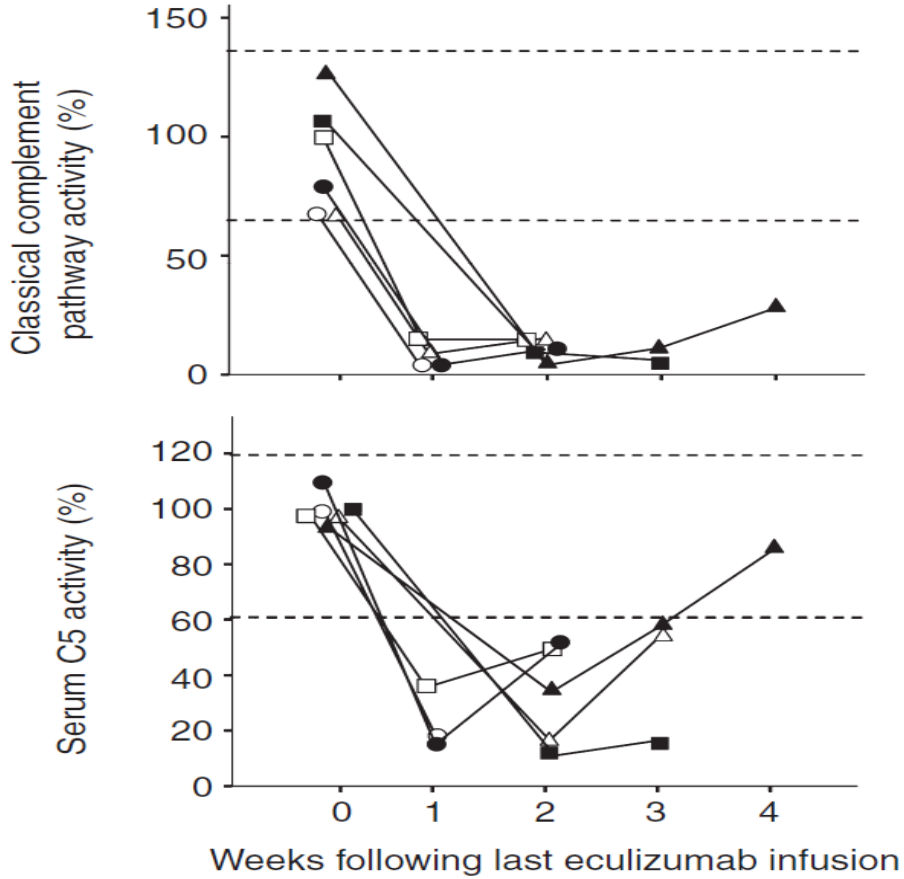
Legendre et al. N Engl J Med, 2013.

Complement-mediated HUS: Treatament

- Eculizumab schedule
  - 900 mg per week for 4 week, then
  - 1200 mg every two weeks

- Reducing/stopping protocols
  - Unknown

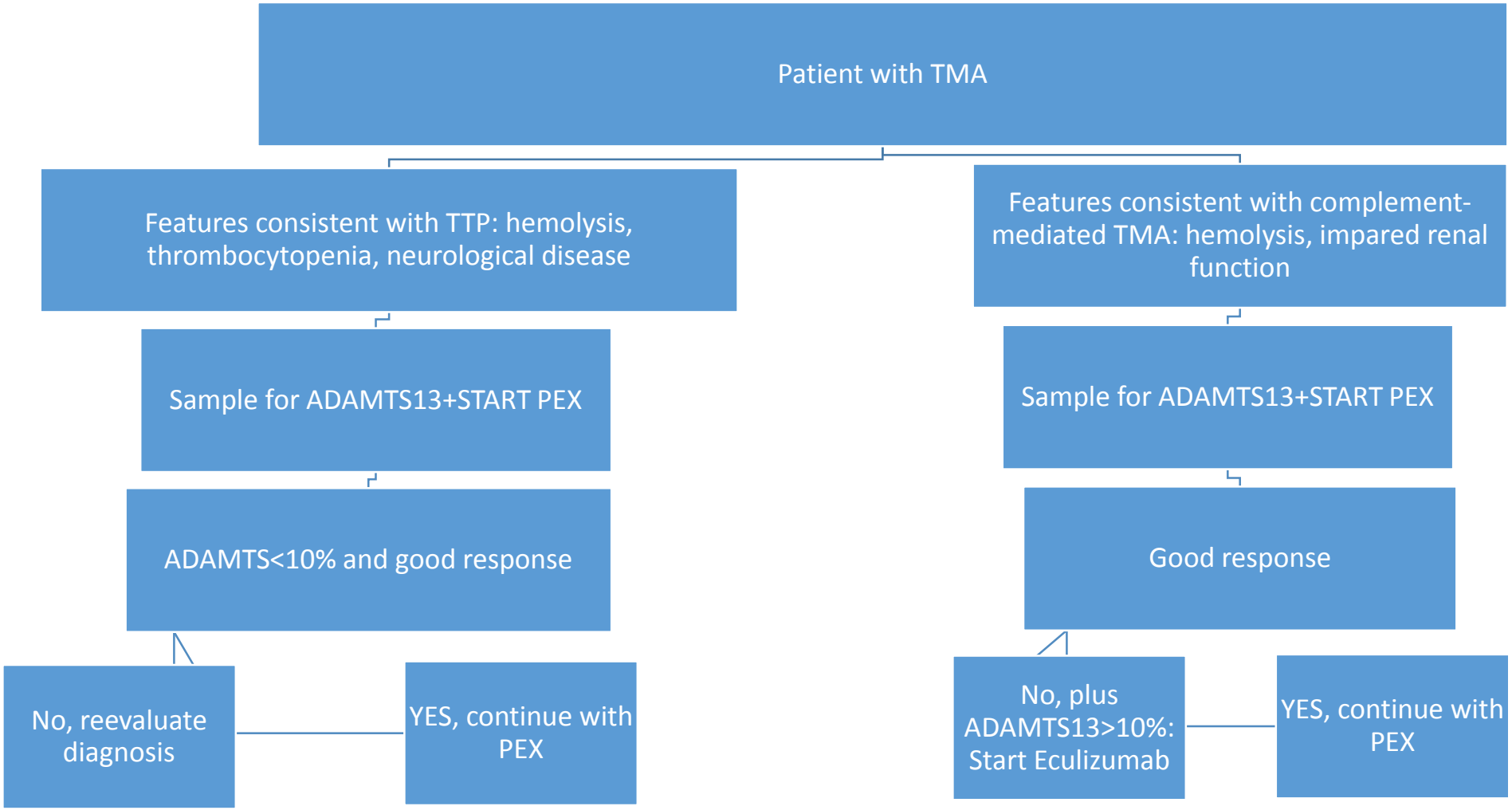
Prolonged complement inhibition in eculizumab-treated aHUS patients



Cugno et al. J Thromb Haemost, 2014.

Conclusions

- Treatment of TTP and HUS
  - Multidisciplinary
  - Intensive
- Advances in pathogenesis, but clinical laboratory testing still not available/standardized
- Close follow-up required


Patient with TMA
Features consistent with TTP: hemolysis, thrombocytopenia, neurological disease
Features consistent with complement-mediated TMA: hemolysis, impared renal function
Sample for ADAMTS13+START PEX
Sample for ADAMTS13+START PEX
ADAMTS<10% and good response
Good response
No, reevaluate diagnosis
YES, continue with PEX
No, plus ADAMTS13>10%: Start Eculizumab
YES, continue with PEX