MAYO CLINIC

TTP and HUS in the Age of Eculizumab

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No conflict of interest

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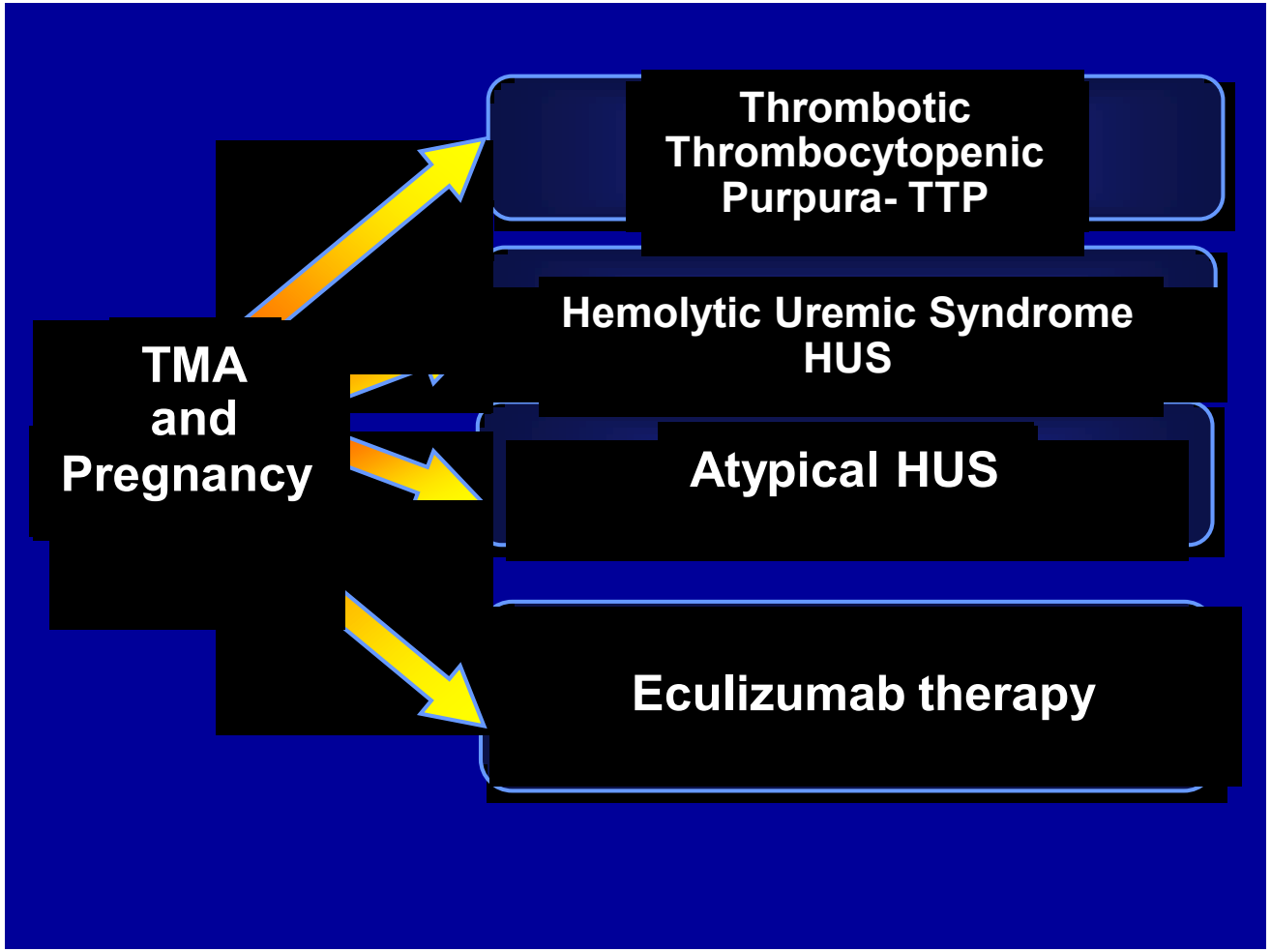
Thrombotic Microangiopathy and Pregnancy



TTP

- Hemolytic Anemia
- Thrombocytopenia
- Ischemic events due to the presence of microvascular occlusive thrombi (↑ vWF multimers)
- Inherited or acquired deficiencies of ADAMTS 13
- TTP pentad
  - MAHA
  - Thrombocytopenia
  - AKI
  - Neurological abnormalities
  - Fever

HUS

- Hemolytic Anemia
- Thrombocytopenia
- 90% associated with diarrhea
  - E colli producing Shiga-like toxin
- 10% atypical HUS due to activation of alternative complement pathway

TTP- HUS

- Acute syndrome with multisystem involvement
  - Thrombocytopenia and microangiopathic hemolytic anemia without an apparent cause
  - Pathologic changes are identical
  - Initial therapy the same: plasma exchange
  - With dominant neurological abnormalities and minimal renal involvement→ classical TTP
  - With minimal neurological involvement and dominant ARF→ HUS
  - “Typical” childhood HUS: abdominal pain and bloody diarrhea

TTP

- Classical features (Moschowitz 1925)
  - Thrombocytopenia
  - Microangiopathic hemolytic anemia (MAHA)
  - Neurologic symptoms and signs
  - Renal failure
  - Fever
- Current trends
  - Diagnostic criteria: dyad of otherwise unexplained thrombocytopenia and MAHA (required for Dx)
  - Classical, “idiopathic”: severe ADAMTS13 deficiency (activity <10%)
  - ADAMTS13 cleaves large vWF multimers
  - Platelet thrombi in the affected organs→ platelet consumption

TTP

- Current trends
  - Inhibitory ADAMTS13 autoantibodies
  - Initiation of plasma exchange: mainstay of therapy
  - 90% mortality to currently curable disease
  - Severe ADAMTS13 deficiency associated with
    - African race
    - Obesity
    - Female sex
    - Other autoimmune manifestations

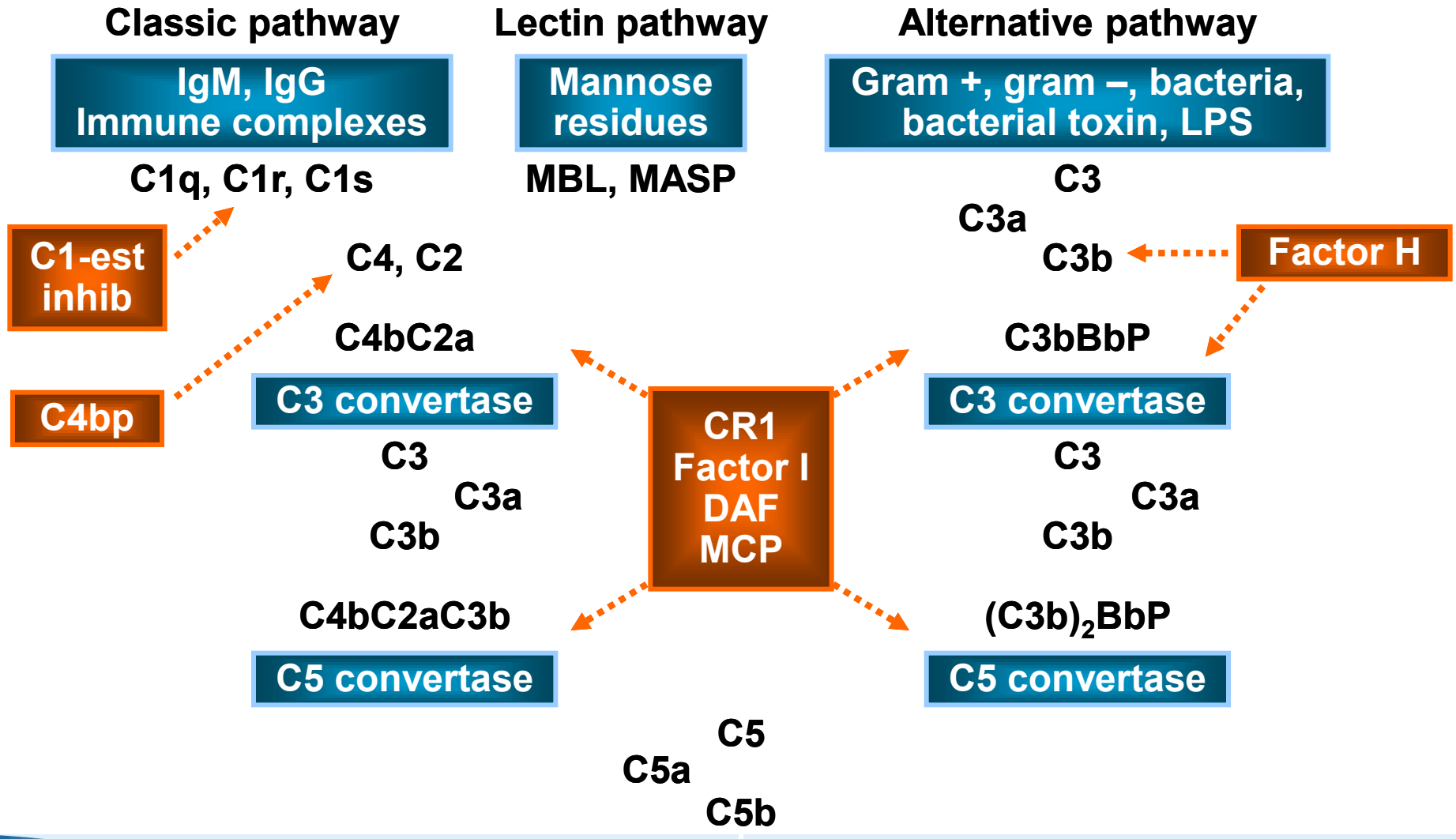
HUS

- Typical childhood HUS 90% of all cases: Shiga toxin producing E. coli (O157:H7) in children (Gasser, 1955)
- Streptococcus pneumoniae
- Under the age of 5 years
- Platelet thrombi occluding vessel lumina

Atypical HUS

- Excessive activation of the alternative C3 convertase leads to complement induced lesions, mainly endothelial cells
- 10% of all cases
- Not caused by an infection
  - Poor prognosis
    - 25% mortality
    - 50% progression to ESRD

Activation Pathways of the Complement System and Their Regulators



Noris and Remuzzi: J Am Soc Nephrol 16:1035, 2005

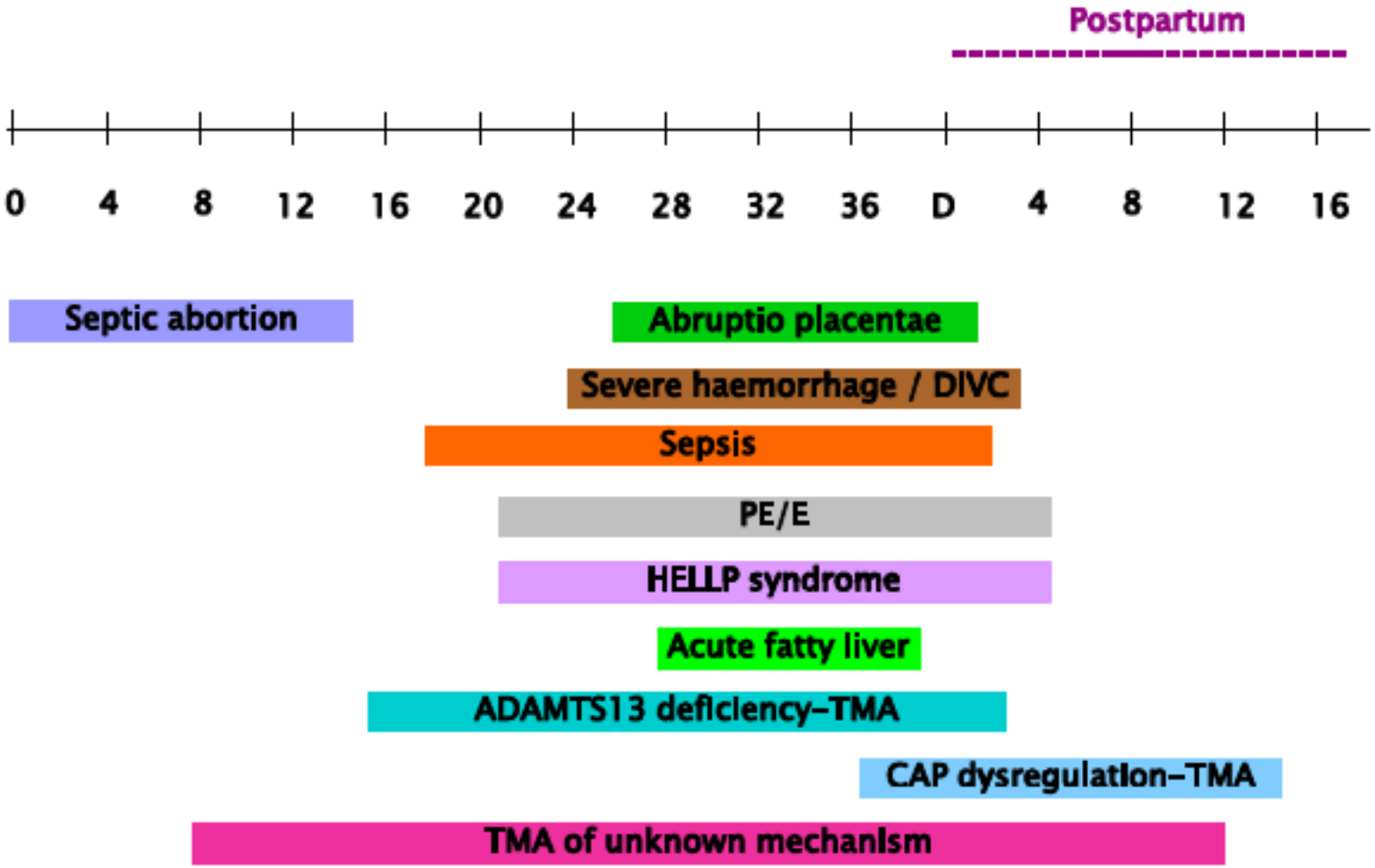
Atypical HUS

- Familial (~20%)
  - Acquired anti-Factor H antibodies
  - Constitutional, inactivating mutations in factors H and I, membrane cofactor protein (MCP), or thrombomodulin
  - Activating mutations in factor B or C3 coding genes (components of the alternative C3 convertase)

Atypical HUS

- Sporadic (~80%)
  - HIV infection
  - Disseminated malignancy
  - Pregnancy
  - Medications
    - Immunosuppressants
    - Antiplatelet agents
  - Systemic disease
    - SLE
    - Scleroderma
    - Antiphospholipid syndrome

Main causes of pregnancy-related AKI

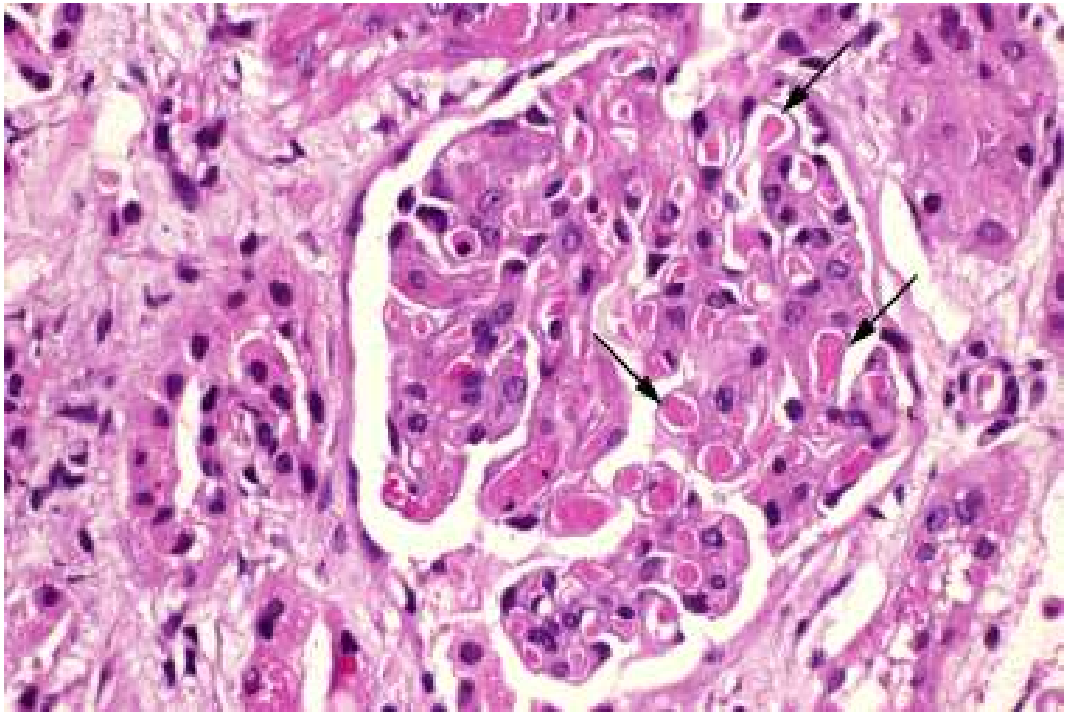


Fakhouri et al CJASN 2012

Thrombotic Microangiopathy and Pregnancy Case 1

- 43-year old, first, twin pregnancy (IVF) admitted at 33 weeks gestation for increasing edema and decreased urinary output
- Lab results: AST 636 u/l, ALT 398 u/l, LDH 1288 u/l, Cr 2.7 mg/dL, thrombocytopenia
- DX: HELLP syndrome Urgent C-section
  - Hemorrhagic shock, multiple transfusions, platelets, FFP, plasmapheresis
- Renal biopsy: TMA

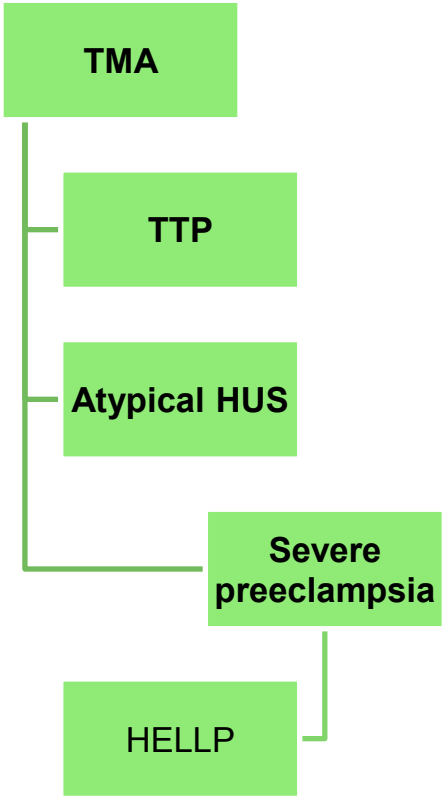
Thrombotic Microangiopathy and Pregnancy: Light Microscopy



Thrombotic Microangiopathy and Pregnancy

- ADAMTS13 levels 45-68%, normal C3, C4, CH50, factors H and I, absent factor H antibody
- Negative mutation analyses
- Positive Lupus anticoagulant
- On chronic HD; evaluated for a RT

Thrombotic microangiopathy (TMA) in Pregnancy



Differential diagnosis: PE/HELLP vs. HUS/TTP

	Preeclampsia	HUS	TTP
Time of onset	late 3rd trimester	postpartum	2nd and 3rd
Renal failure	unusual	common	minimal or absent
Renal prognosis	recovery	75% ESRD	fair
Neurological findings	present	minimal or absent	dominant
Low platelet count	present (HELLP)	present	present
DIC	present	absent	absent
Abnormal LFT	present (HELLP)	absent	absent
Complement alternative pathway	present (HELLP)	present	absent
↓ ADAMTS13	mild to moderate	absent	severe

Smyth and Garovic. Glomerular disease in pregnancy. In Core concepts in parenchymal kidney disease. Springer, 2014

Pregnancy-associated atypical HUS

- Atypical HUS in 100 adult female patients
  - Pregnancy-associated, n=21
- 79% presented postpartum
- Moderate thrombocytopenia (>100K in 40%)
- No neurological signs/symptoms
- Renal biopsy (8/21): Arteriolar and capillary thrombi, “double contour,” mesangiolysis
- Alternative complement pathway gene mutations in 18 of the 21
  - 76% ESRD by last follow-up

Fakhouri et al. JASN, 2010

Pregnancy-associated atypical HUS

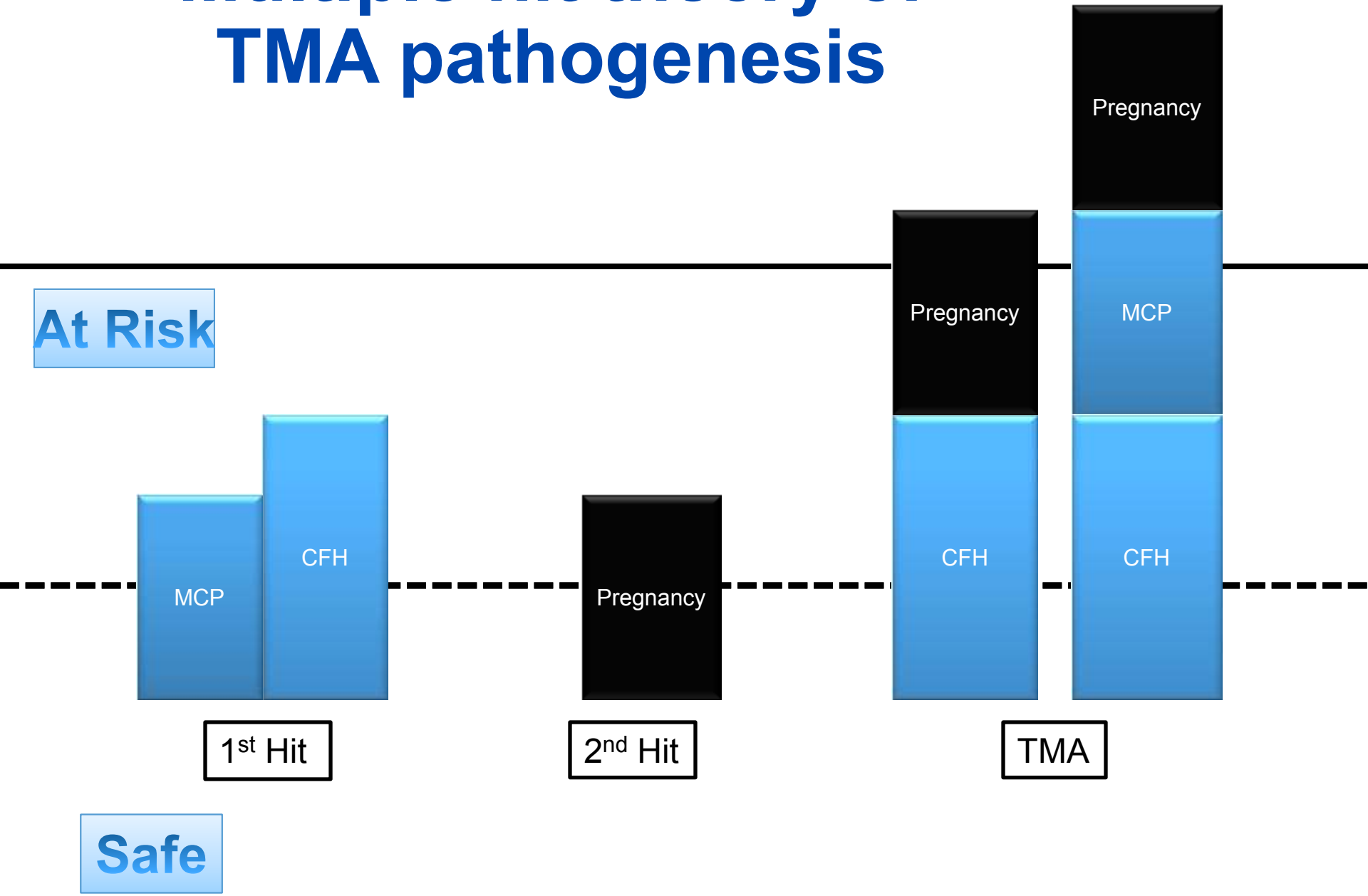
Table 4. Frequency of P-aHUS according to the type of complement dysregulation

Patients	Number of Pregnancies	P-aHUS (%)
CFH mutations ($n = 23$)[a]	49	10 (20%)
Mutations in SCR19-20 ($n = 6$)	10	1 (10%)
Mutations in other SCR ($n = 17$)	38	9 (24%)
CFI mutations ($n = 8$)	26	3 (11%)
MCP mutations ($n = 4$)	6	1 (17%)
C3 mutations ($n = 3$)	7	2 (28%)
CFB mutations ($n = 2$)	7	0 (0%)
More than one mutation ($n = 4$)[b]	5	3 (60%)
No mutation ($n = 10$)	15	3 (20%)

[a]Three patients with two mutations in CFH (SCR 9 and 19)—in C3/CFH and in MCP/CFH—were excluded from the analysis.
[b]Patients with two mutations in CFH (SCR 9 and 19)—in C3/CFH (patient 8), in MCP/CFH (P3), and in CFI/CFI (patient 4).

Fakhouri et al. JASN, 2010

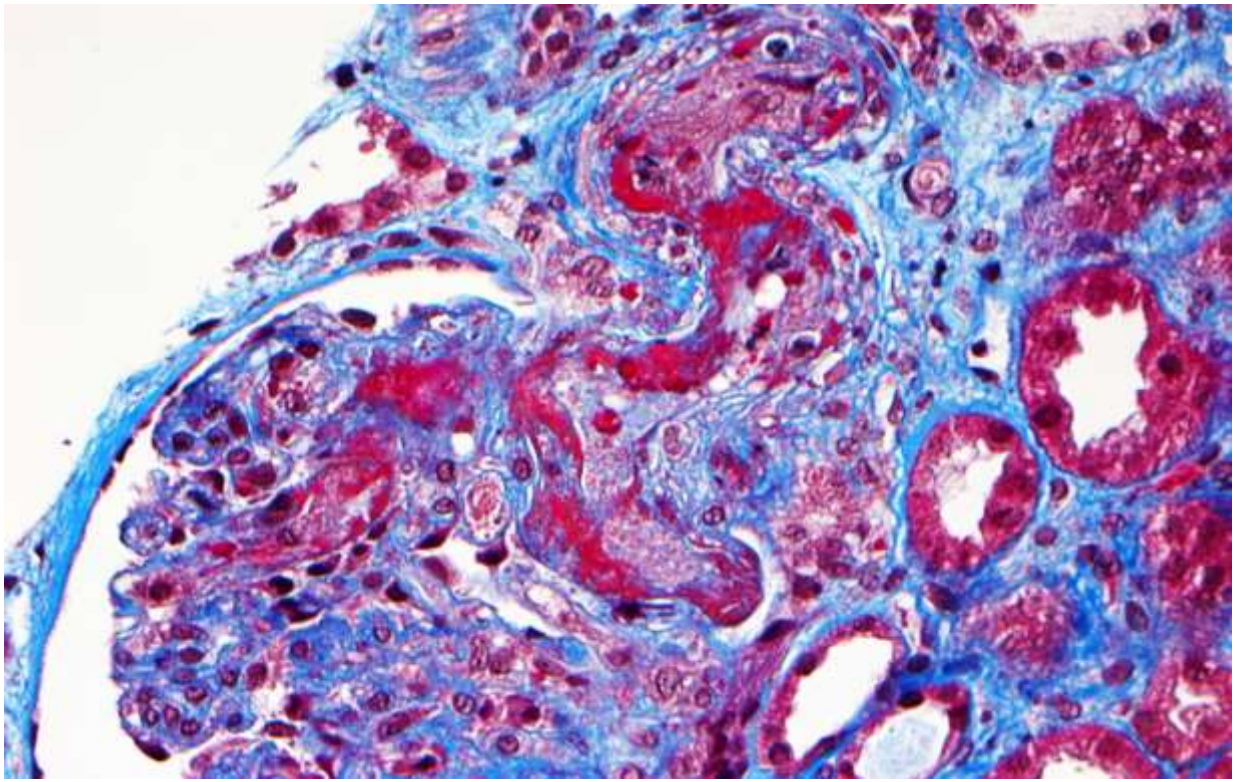
Multiple hit theory of TMA pathogenesis



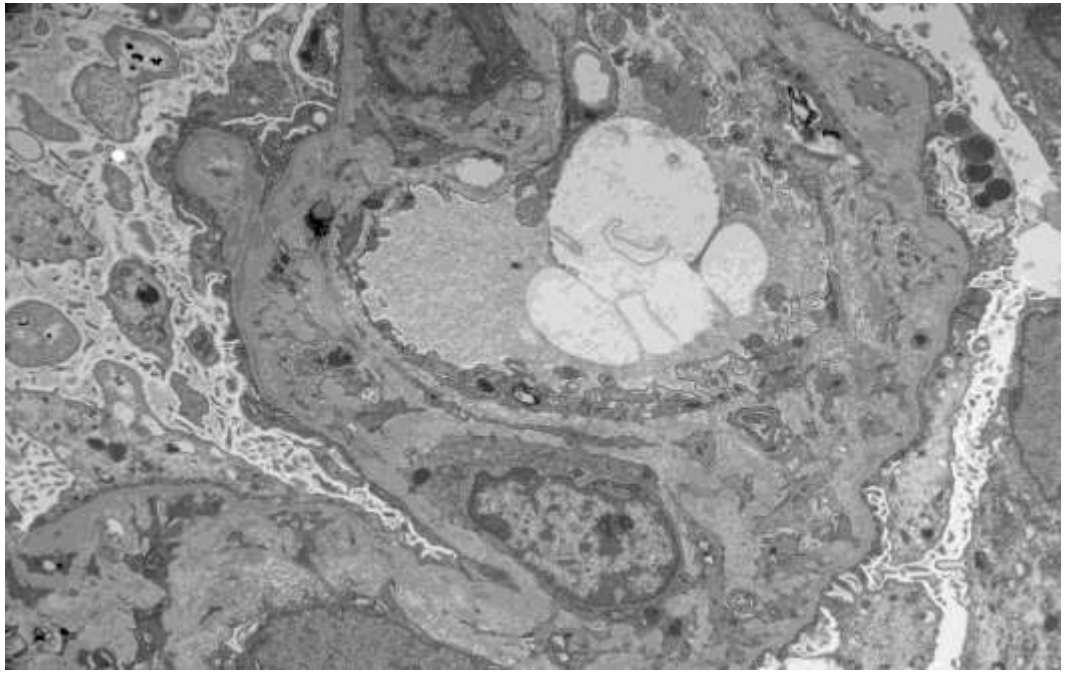
Thrombotic Microangiopathy and Pregnancy Case 2

- 18-year old, biopsy proven IgA nephropathy, with a baseline Cr of 1.7 mg/dL
- Presented 15 weeks pregnant, Cr of 7.0 mg/dL
- Hemodialysis initiated
- Renal US: normal kidney size
- Renal biopsy performed

Case 2: TMA and Pregnancy



Case 2: TMA and Pregnancy



Thrombotic Microangiopathy and Pregnancy Case 2

- Testing for complement factors I and H, membrane cofactor protein and C3 negative
- Positive for a heterozygous mutation in thrombomodulin
- Mother detected as a carrier
- Postpartum received a living related kidney transplant from her father
- Stable with a Cr of 1.5 mg/dL

Treatment

- Plasma exchange or plasma infusion
- Immunosuppressant drugs
- Renal transplant: high recurrence rates other than in MCP -highly expressed in kidneys-
  - Consideration of kidney/liver transplant
- A human plasma-derived CFH is being developed
- Eculizumab- a humanized anti-C5 monoclonal antibody

Eculizumab

- .1st in-class humanized monoclonal anti-C5 antibody
- Paroxysmal nocturnal hemoglobinuria (PNH), a complement-induced hemolytic anemia
  - ↓ frequency of hemolysis, hemoglobinuria, transfusion, and thrombosis
    - *Hillemen et al. NEJM, 2006*
- Additional indications considered

Eculizumab in pregnancy

- Pregnant women with PNH
- PNH associated with ↑ maternal and fetal complications
  - Thrombotic events
  - Infections
  - Bleeding
  - Anemia
  - Miscarriages
  - Fetal death
  - Prematurity
  - ? Pregnancy contraindicated

Eculizumab in pregnancy

- Case reports and case series of Eculizumab for PNH in pregnant women
  - May need ↑ dose to block complement in late pregnancy
  - Safe for newborns (no complement blockade in umbilical cord blood samples)
  - May reduce PNH-related complications in pregnancy
    - *Kelly et Al. BJH, 2010*

Eculizumab in pregnancy

- Women with PNH
- Does not affect newborns
  - Eculizumab-C5 complex present in traces
  - Complement activity normal, while mothers lacked terminal complement pathway activity
- Eculizumab does not impair the complement function in newborn

Hallstensen et al. Immunobiology, 2014

Eculizumab in pregnancy

- Approved fro the treatment of atypical HUS in the US and Europe in 2011
- Used judiciously in pregnancy-case reports
- First case
  - 26-year old with homozygous mutation in CFH
  - Developed a relapse of aHUS at 17 GW
  - Received PEX and Eculizumab starting at 26 GW
  - Achieved remission and delivered healthy baby at 38 GW

Ardissino et al. ACOG, 2013

Eculizumab in pregnancy

- 2nd case
  - 32-year old presented at delivery with anemia, thrombocytopenia and renal failure
  - Underwent C-section and hysterectomy due to severe bleeding
  - Treated with PEX, steroids, and Eculizumab with normalization of renal function
  - Genetic testing negative, Eculizumab discontinued after treatment x 6 months
  - Patient remained in remission 1 year post Dx

Canigral et al. Ann Hematol, 2014

Eculizumab for preeclampsia/HELLP

- 3rd case
  - 35-year old presented at 26 GW with severe HELLP
  - Treatment with Eculizumab initiated
  - Initially, worsening HTN and pulmonary edema
  - Subsequently, markers of hemolysis, LFTs and thrombocytopenia improved
  - Pregnancy was prolonged for 17 days, C-section at 29 GW for worsening HTN and proteinuria
  - The cord blood Eculizumab level 20X lower than in the maternal blood (too low to block complement)
  - No detectable Eculizumab in the breast milk

Burwick and Feinber. Placenta, 2012

aHUS mutations in preeclampsia/HELLP

- 4/11 patients with HELLP and renal involvement had mutations in the alternative complement pathway genes

Fakhouri et al. Blood, 2008

- Among 40 patients with SLE and/or APL Ab who developed preeclampsia, 7 (18%) were heterozygous for MCP, CFI, or CFH mutations. Among 59 women with preeclampsia, but without autoimmune disorders, 5 (8%) were heterozygous for these mutations.

Salmon et al. PLOS Medicine, 2011

Eculizumab for aHUS in pregnancy

- Availability of Eculizumab will make child bearing safer for patients with aHUS
- More evidence on its use in this setting is needed (? multicenter study)
- Question: would Eculizumab be effective in a subset of preeclampsia/HELLP patients with mutations in the alternative complement pathway genes?
- The medication cost may be justifiable in cases of recurrent pregnancy losses due to early and severe preeclampsia/HELLP

Questions?

Eculizumab for aHUS in pregnancy

- 38-year old, para 5, 09/15
- Presented at 34 weeks with HTN, Cr of 2.3 mg/dL and low platelet count (<50K)
- Renal biopsy not performed
- ADAMTS13 normal
- Initiated on Eculizumab; received 2 doses
- Creatinine remained elevated, 2.7 mg/dL
- Second opinion

Eculizumab for aHUS in pregnancy

- Renal biopsy: 50% focal global glomerulosclerosis with moderate interstitial fibrosis and tubular atrophy with inflammation
- Genetic testing:
  - Heterozygous for CFH polymorphism that is common in healthy, but enriched in aHUS population
  - Heterozygous for the large CFHR1-CFHR3 deletion (but, only homozygous deletions have been associated with CFH auto-antibodies and aHUS