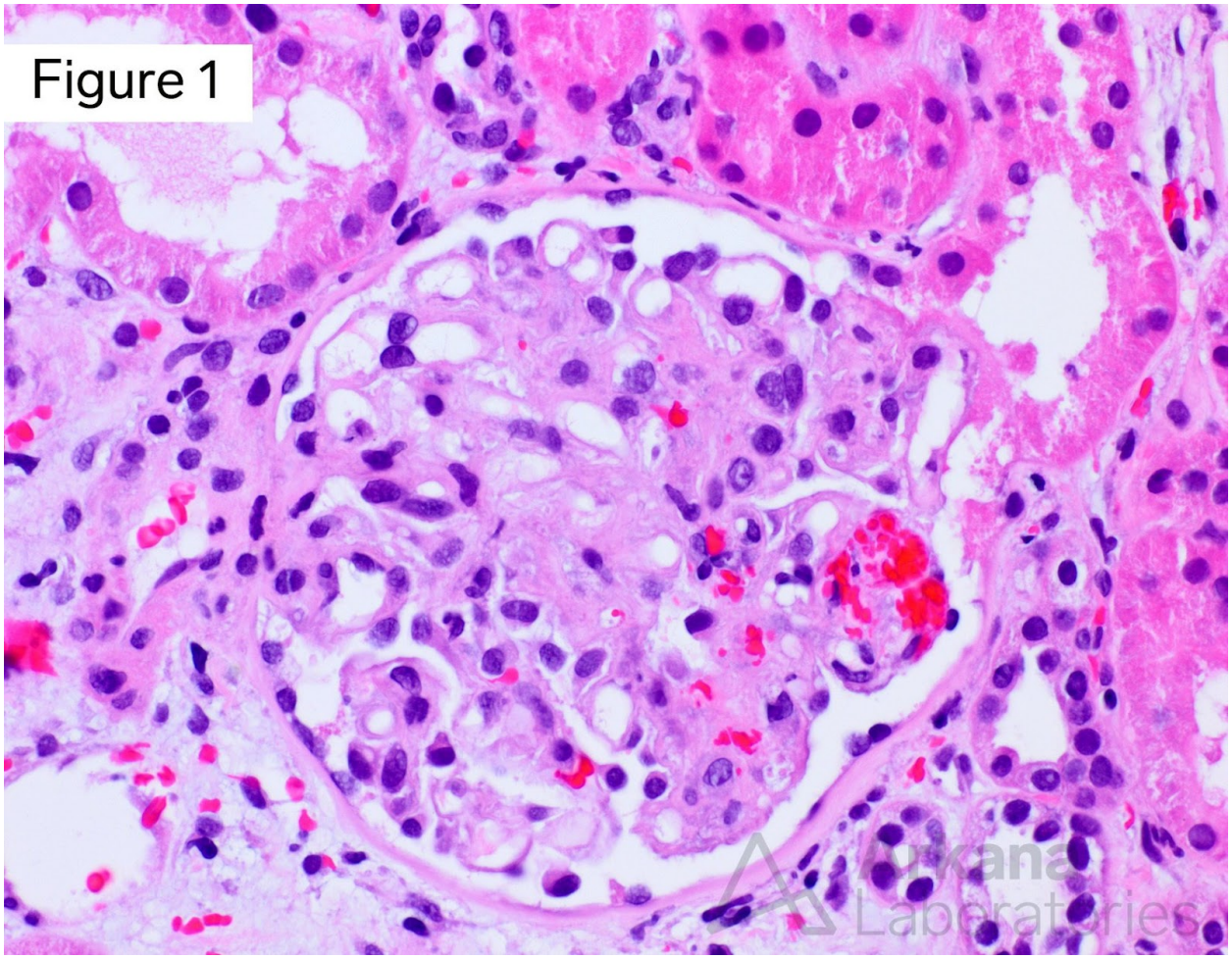
1/ 🚨 📣 Tweetorial Alert !
Hey #NephTwitter, today we will discuss Thrombotic microangiopathy (TMA) in pregnancy from the recently published review in @KIReports
https://www.kireports.org/article/S2468-0249(24)01739-X/pdf by @ManuelUrra7 @RichardBurwick @CTeodosiu @anuja_java

2A/ What is TMA?
It is a clinicopathological entity characterized by
👉Microangiopathic hemolytic anemia: Hgb< 10^9 g/dl, LDH >1.5 X upper limit of normal, schistocytes +
👉Platelets <150*10/L
👉End organ damage: renal, cardiac and nervous system

2B/ Renal histopathology in TMA?
🔬 Light microscopy- fibrin thrombi within the glomeruli
🔬 Non thrombotic features- endothelial swelling, mesangiolysis (in picture), double contours in GBM
Let's check out the image from @arkanalabs
https://www.arkanalabs.com/diagnose-this-august-22-2022/



2C/ Vascular changes in TMA?
👉Intramural fibrin deposition, myxoid intimal thickening, myo-intimal proliferation (onion-skinning) may occur
Let's look at the figure from @RenalFellowNtwk
https://www.renalfellow.org/2020/10/02/kidney-biopsy-of-the-month-thrombotic-microngiopathy/

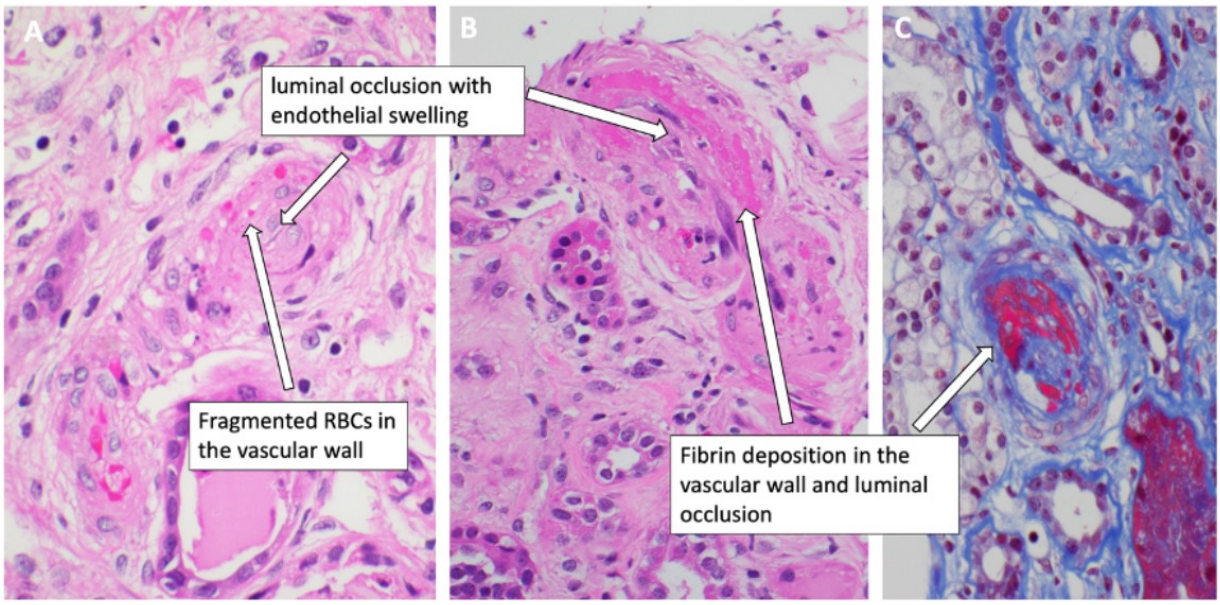
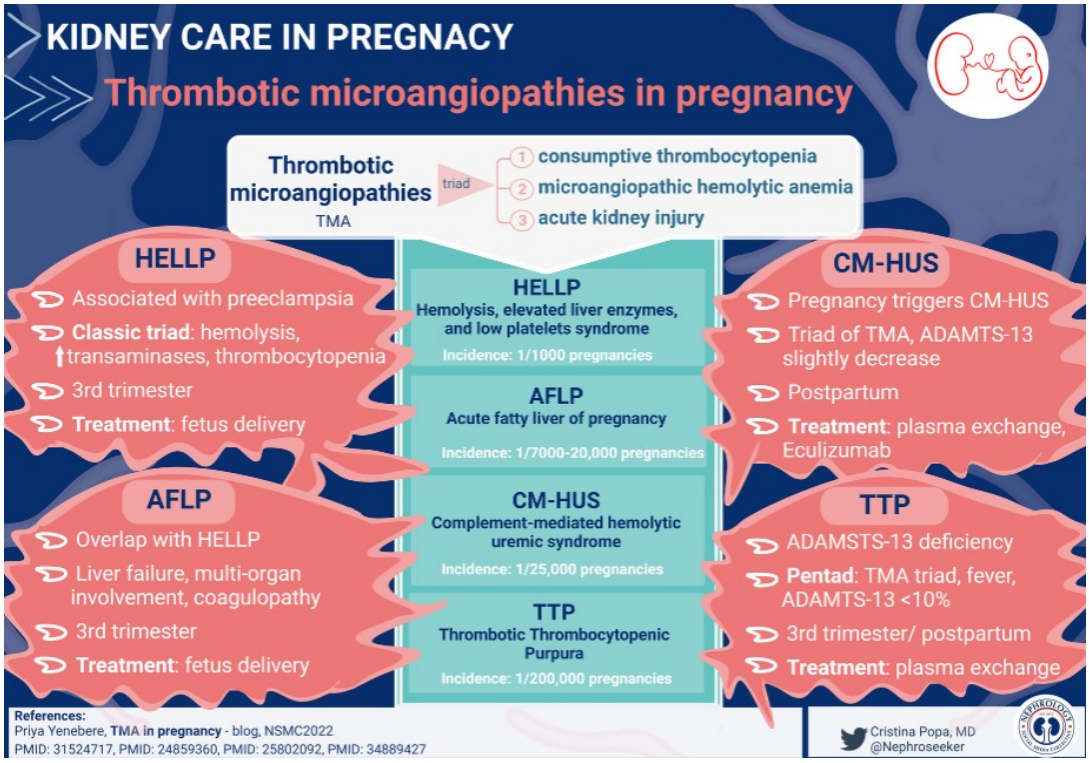


Figure 6: Vascular changes in acute TMA A) fragmented red blood cells entrapped in vascular wall (H&E) B) Fibrinoid necrosis in arteriolar vessel wall and luminal occlusion with endothelial swelling (H&E) C) One arteriole with fibrin thrombi (bright red color on MTC)

3A/ Now, coming to our topic TMA in pregnancy (p-TMA), let's start with a poll: What are the major forms of p-TMA?
A/ Thrombotic thrombocytopenic purpura (TTP)
B/ HELLP syndrome
C/ Complement mediated TMA (CM-TMA) or aHUS
D/ TMA associated with antiphospholipid syndrome (APS)
E/ All of the above

3B/ The correct answer is E. Let's look at the beautiful infographic by @Nephroseeker



4/ Outcome of p-TMA:
🚨4.5 times increased risk of mortality
🚨81% of patients require dialysis
🚨46% progress to end-stage kidney disease

5A/ Let us discuss the 4 major causes of p-TMA separately

🚩**TTP** - Incidence
👉Occurs at a rate of 2 in 100,000 pregnancies
👉Accounts for 12-25% of adult-onset TTP cases
👉May be congenital (cTTP) or acquired/immune (iTTP)

5B/ TTP- Pathophysiology
🚫Deficiency in ADAMTS13 → uncleaved ultra large VWF multimers → microthrombi
🚫cTTP- recessive mutation in ADAMTS13 gene
🚫iTTP- acquired autoantibodies + (anti ADAMTS13 IgG + in 75% cases)
https://www.kireports.org/article/S2468-0249(24)01739-X/pdf

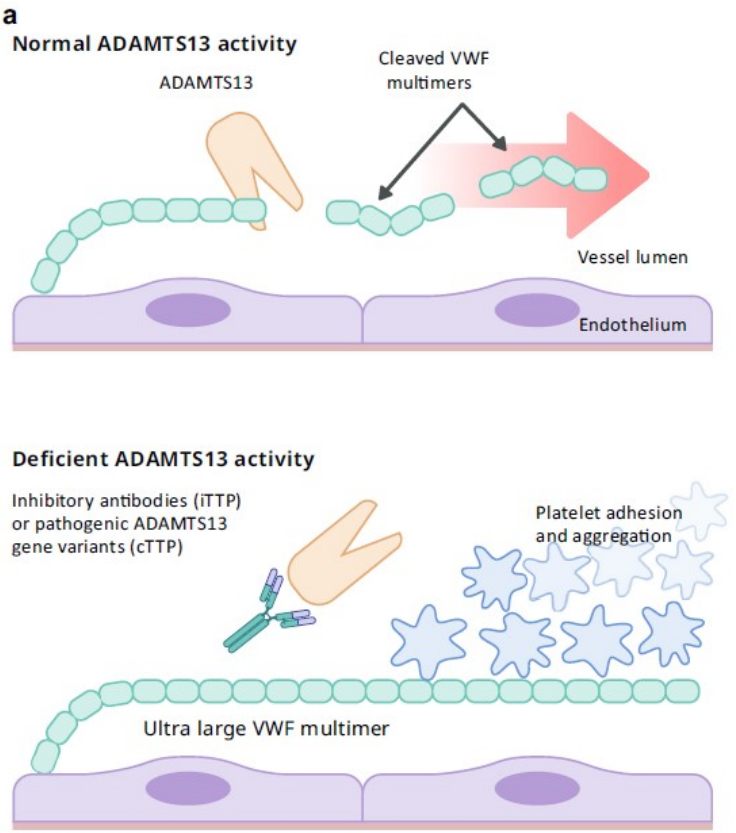


Figure 1. (a) Pathogenesis of Thrombotic Thrombocytopenic Purpura (TTP). ADAMTS13 is a plasma protease that cleaves ultra large VWF multimers into smaller multimers. Deficient enzymatic activity (caused by either inhibitory antibodies or pathogenic gene variants) leads to accumulation of ultra large multimers on the endothelial surface, providing a scaffolding for platelets to attach. ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; cTTP, congenital TTP; iTTP, immune TTP; VWF, von Willebrand Factor. (Continued)

5C/ 🤰 In pregnancy: VWF levels ⏫ as early as 1st trimester → consumptive decrease in ADAMTS 13 → unmasking of cTTP
👉Incidence of cTTP: 24-66% in all pregnancy related TTP cases

5D/ The following infographic summarizes the clinical features and diagnosis of TTP

Thrombotic thrombocytopenic purpura

CLINICAL FEATURES	DIAGNOSIS
Most common in 3rd trimester and postpartum	**Diagnosis of iTTP-** ADAMTS13 activity level <10% ADAMTS 13 IgG +
Fever	**Diagnosis of cTTP-** ADAMTS13 activity level <10% Absence of ADAMTS13 IgG Mutation positive
Neurologic manifestation **Stronger** association Encephalopathy, seizures, CVA	Plasmic Score – differentiate high risk score (>5) versus intermediate-low risk score
Renal injury – mild	@KajareeG
Severe thrombocytopenia (<30,000/uL)	

5E/ Treatment: iTTP

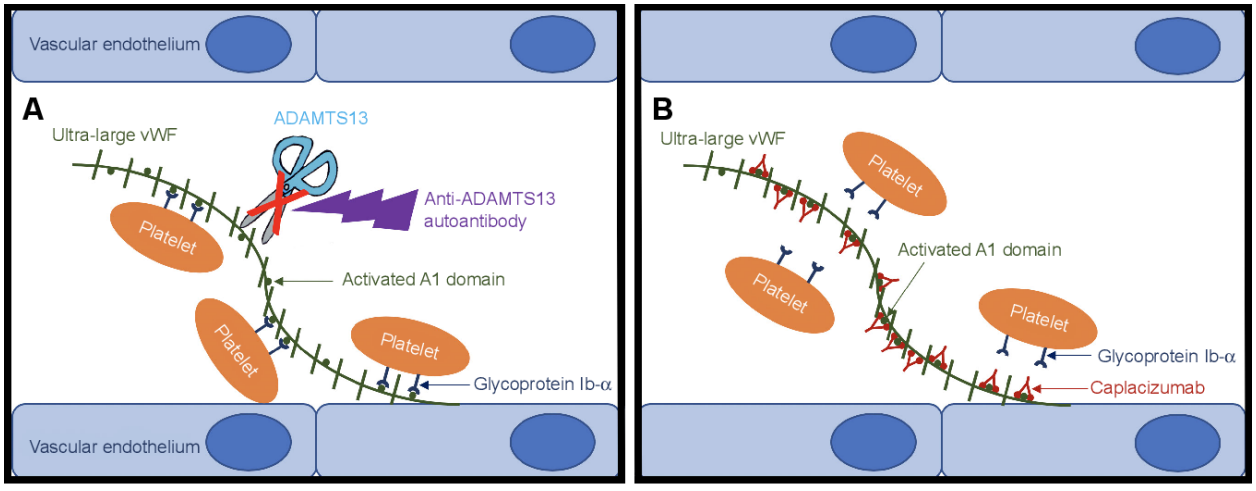
- Daily plasma exchange PLEX- 1-1.5X plasma volume using FFP; continue for minimum 2 days after remission (normalization of neurologic status/platelets/LDH)
- Prompt initiation of PLEX increases survival rate 80-90%
- Oral prednisone- 1 mg/kg/day

5F/ 💥New therapy: Caplacizumab

👉Monoclonal antibody against VWF; blocks the adhesion of VWF multimers to platelets

👉Use in a pregnant patient with TTP refractory to both PLEX and corticosteroids resulted in hematological recovery and successful delivery

https://pubmed.ncbi.nlm.nih.gov/37226361/



5G/ Treatment: cTTP
🚩FFP (10-15 ml/kg every 2 weeks) which replaces deficient levels of ADAMTS13
🚩PLEX in severe cases
🚩Maintain ADAMTS13 activity >20-25%

5H/ 💥New therapy: Recombinant ADAMTS13
👉A phase 3, open label, cross over trial with 48 cTTP patients @NEJM
👉Mean maximum ADAMTS 13 activity in the prophylactic recombinant ADAMTS13 group was 101%, no acute TTP event
https://www.nejm.org/doi/abs/10.1056/NEJMoa2314793

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Recombinant ADAMTS13 in Congenital Thrombotic Thrombocytopenic Purpura

Scully M et al. DOI: 10.1056/NEJMoa2314793

CLINICAL PROBLEM

Congenital thrombotic thrombocytopenic purpura (TTP) results from severe hereditary deficiency of ADAMTS13, leading to widespread thrombosis, multiorgan dysfunction, and premature death. Data comparing recently approved recombinant ADAMTS13 treatment with standard therapy, which requires infusion in the hospital and carries a high risk of allergic reactions to plasma, are lacking.

CLINICAL TRIAL

Design: A prespecified interim analysis of a phase 3, multicenter, open-label, randomized, controlled, crossover trial assessed the efficacy and safety of prophylaxis with recombinant ADAMTS13 (rADAMTS13) among children and adults with congenital TTP.

Intervention: 48 patients were randomly assigned to 6 months of prophylaxis with rADAMTS13 (40 IU per kilogram of body weight, administered intravenously) or standard therapy with plasma-derived products (period 1), followed by 6 months of the alternate treatment (period 2), followed by another 6 months of prophylaxis with rADAMTS13 (period 3). The primary outcome was acute TTP events.

RESULTS

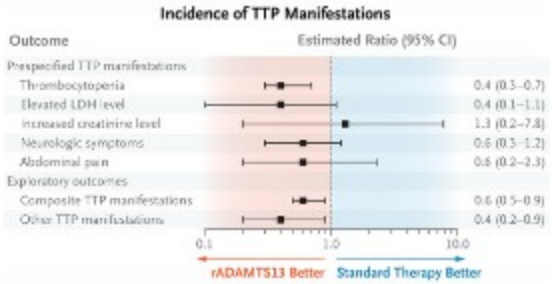
Efficacy: No patients had an acute TTP event while receiving rADAMTS13, whereas one patient had an acute TTP event while receiving standard therapy. In addition, results for TTP manifestations such as thrombocytopenia suggested improvements with rADAMTS13.

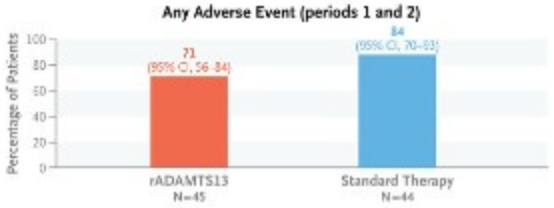
Safety: Overall, rADAMTS13 had a better safety profile than standard therapy.

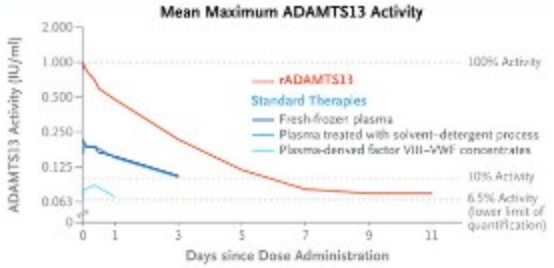
LIMITATIONS AND REMAINING QUESTIONS

- Owing to the rarity of congenital TTP, the trial did not have sufficient power to enable statistical hypothesis testing.
- The trial had an open-label design.
- The efficacy analyses focus on adults and adolescents, because the available data from pediatric patients were limited by age-staggered enrollment.

Links: Full Article | NEJM Quick Take







CONCLUSIONS

Among patients with congenital TTP, rADAMTS13 was an effective prophylactic therapeutic approach with an acceptable side-effect profile.

This Research Summary was updated on May 14, 2024, at NEJM.org.

5 I/ 🚨 TTP: outcomes

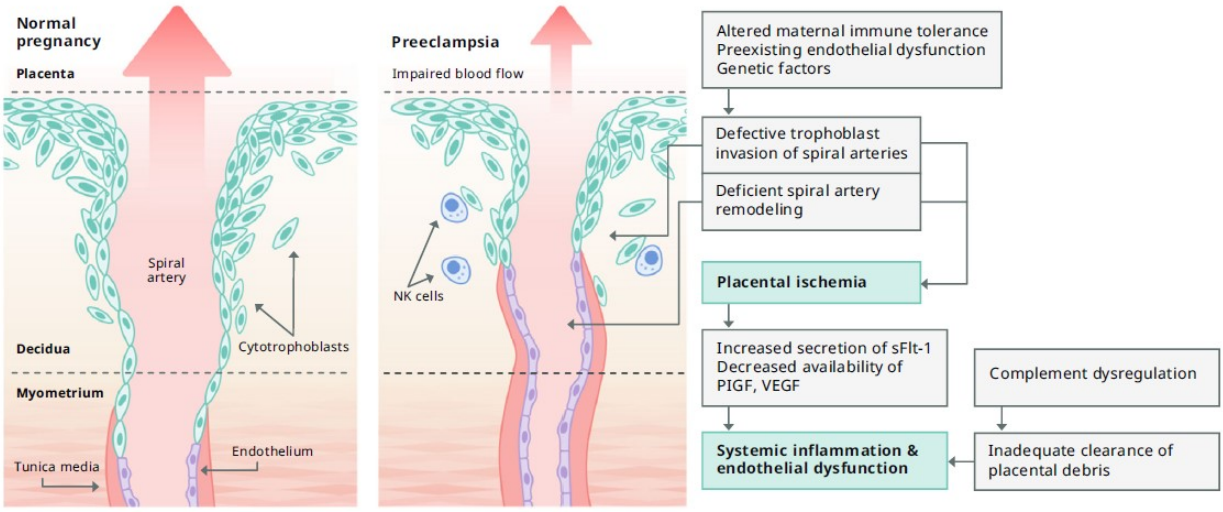
🚨Maternal: stroke, myocardial infarction, acute kidney injury, disseminated intravascular coagulation, relapsing TTP

🚨Fetal: placental infarction, death

6A/ **HELLP SYNDROME**: Incidence
👉Most common cause of p-TMA; 0.5-1% of all pregnancies
👉>⅔ rd cases in third trimester;
⚡Maternal mortality rate 1.1%; prenatal death rate 7-34%

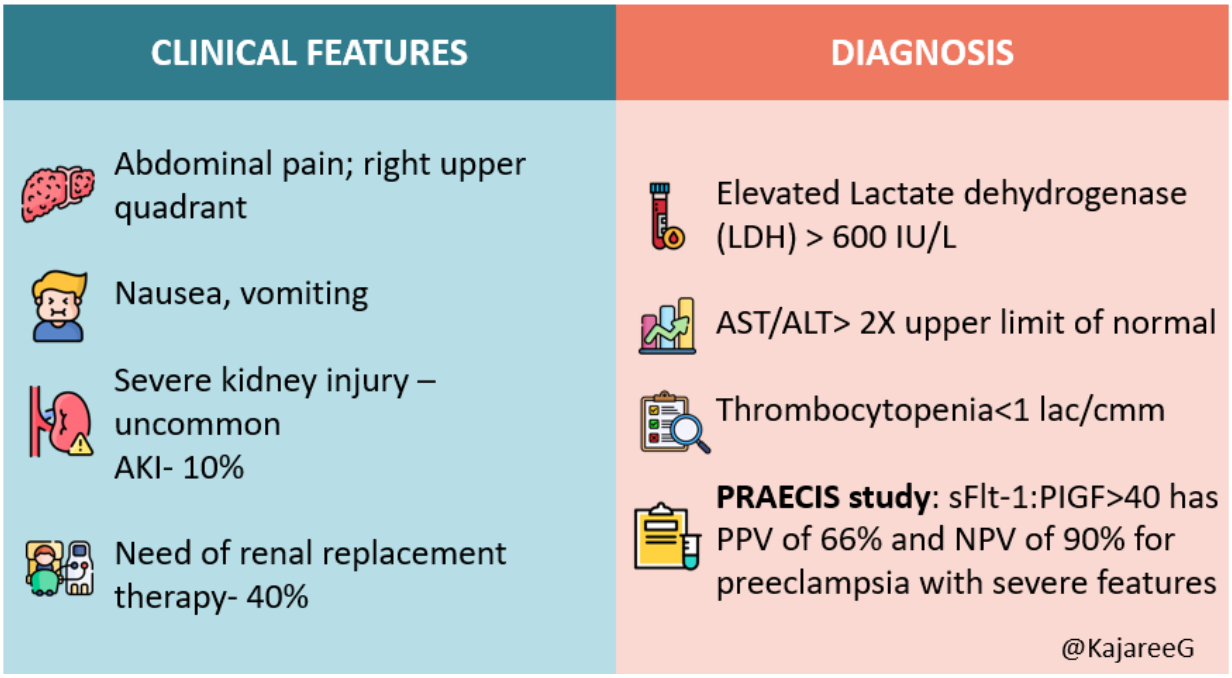
6B/HELLP: pathophysiology
🤰 In pregnancy: dysregulated complement system + abnormal placentation → ⏫in C5a and C5b-9
🧬Genetic mutations in factor H,factor I, membrane cofactor protein or C3 - in 45% cases of HELLP

Check out this wonderful infographic from the review



6C/ HELLP
👀The following infographic summarizes the clinical features and diagnosis of HELLP syndrome

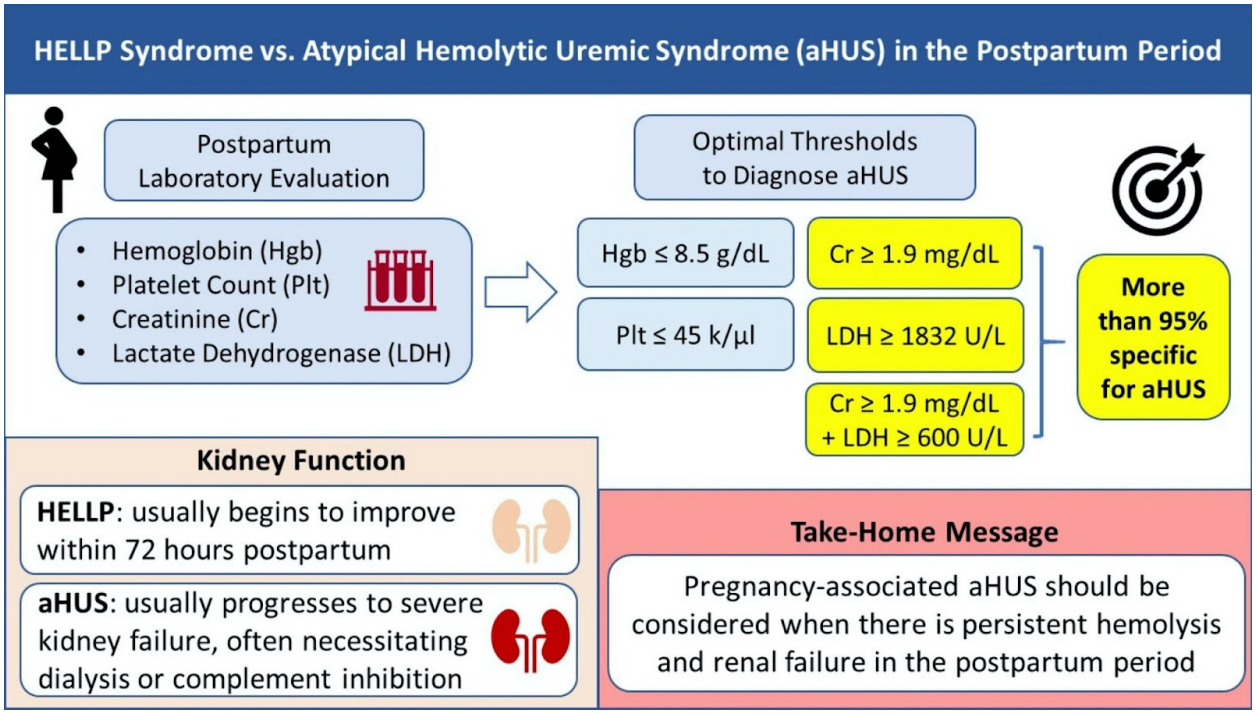
HELLP SYNDROME



6D/ HELLP: Treatment

- Delivery of the fetus and placenta
- HELLP resolves within 3-4 days of delivery
- A recent study by @anuja_java in @Hypertension concluded that serum creatinine and LDH help to differentiate HELLP from CM-TMA

https://pubmed.ncbi.nlm.nih.gov/34275337/

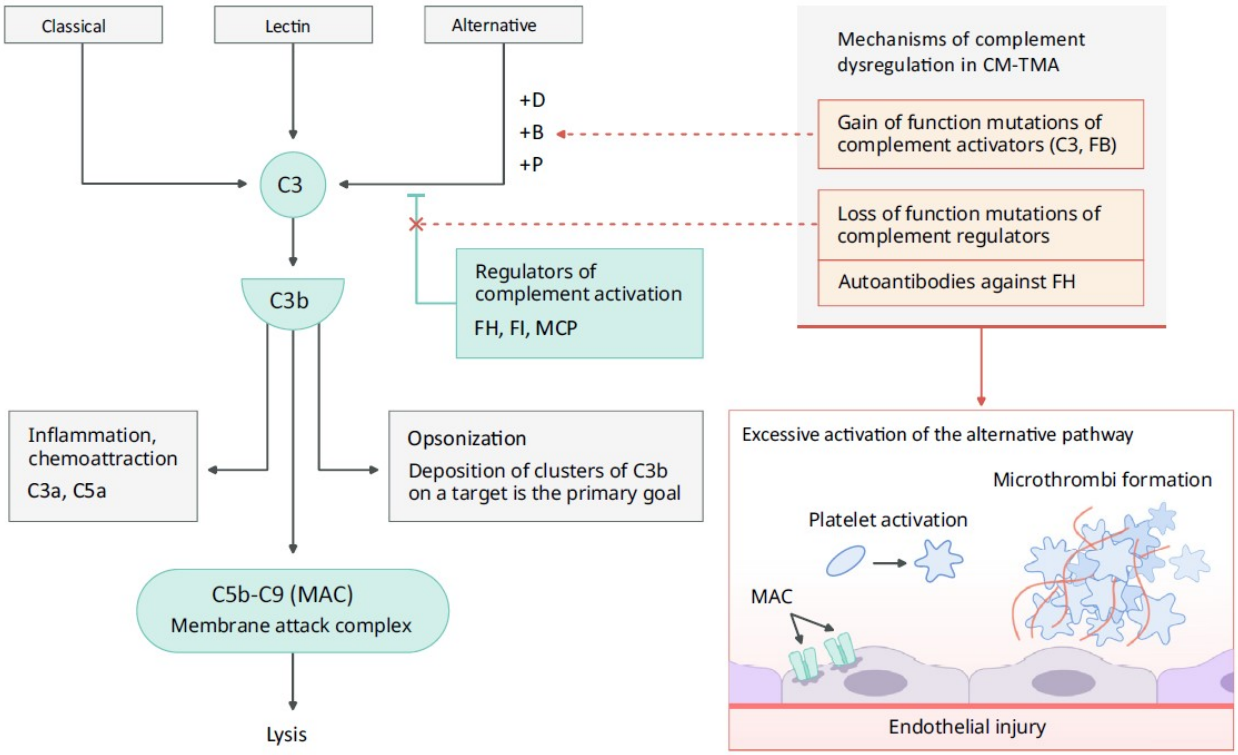


6E/ HELLP: Outcomes
🚨Maternal: ⏫ risk of development of preeclampsia and HELLP in subsequent pregnancies, hypertension, seizures, stroke, pulmonary edema, cardiovascular disease
🚨Fetal: intrauterine growth restriction, prematurity

7A/ CM-TMA: Incidence
👉Pregnancy related CM-TMA occur in 1 in 25000 pregnancies; account for 7% of all TMA cases
👉79% present in the postpartum period

7B/ CM-TMA: Pathophysiology
⏫Overactivation of the alternative pathway of complement
🧬Heterozygous loss of function mutation in factor H, factor I or membrane cofactor protein (MCP, CD46) - in 60-70% of patients

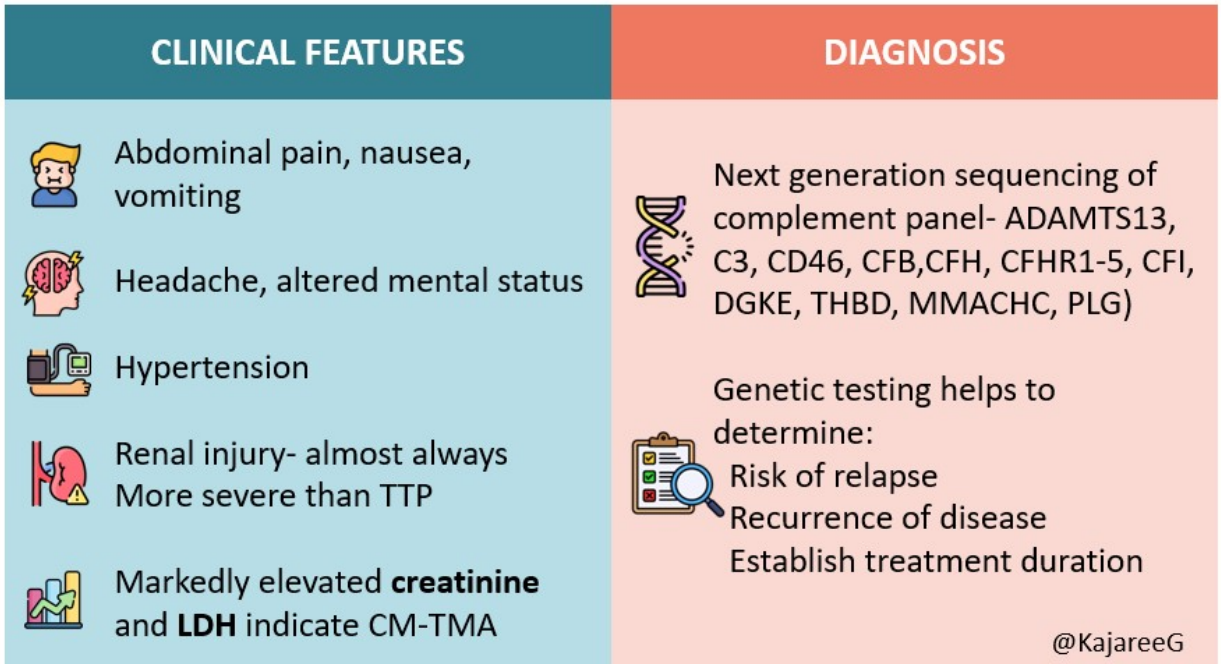
Check out this beautiful infographic from the review



7C/
🤰 Pregnancy is an immune privileged condition
⚡ The regulators of complement activation (decay accelerating factor- DAF, CD55, MCP, CD59) prevent placental damage during pregnancy
⚡ In postpartum period- reversal of this phenomenon predispose to CM-TMA

7C/ CM-TMA:
👌 The following infographic summarizes the clinical features and diagnosis of CM-TMA

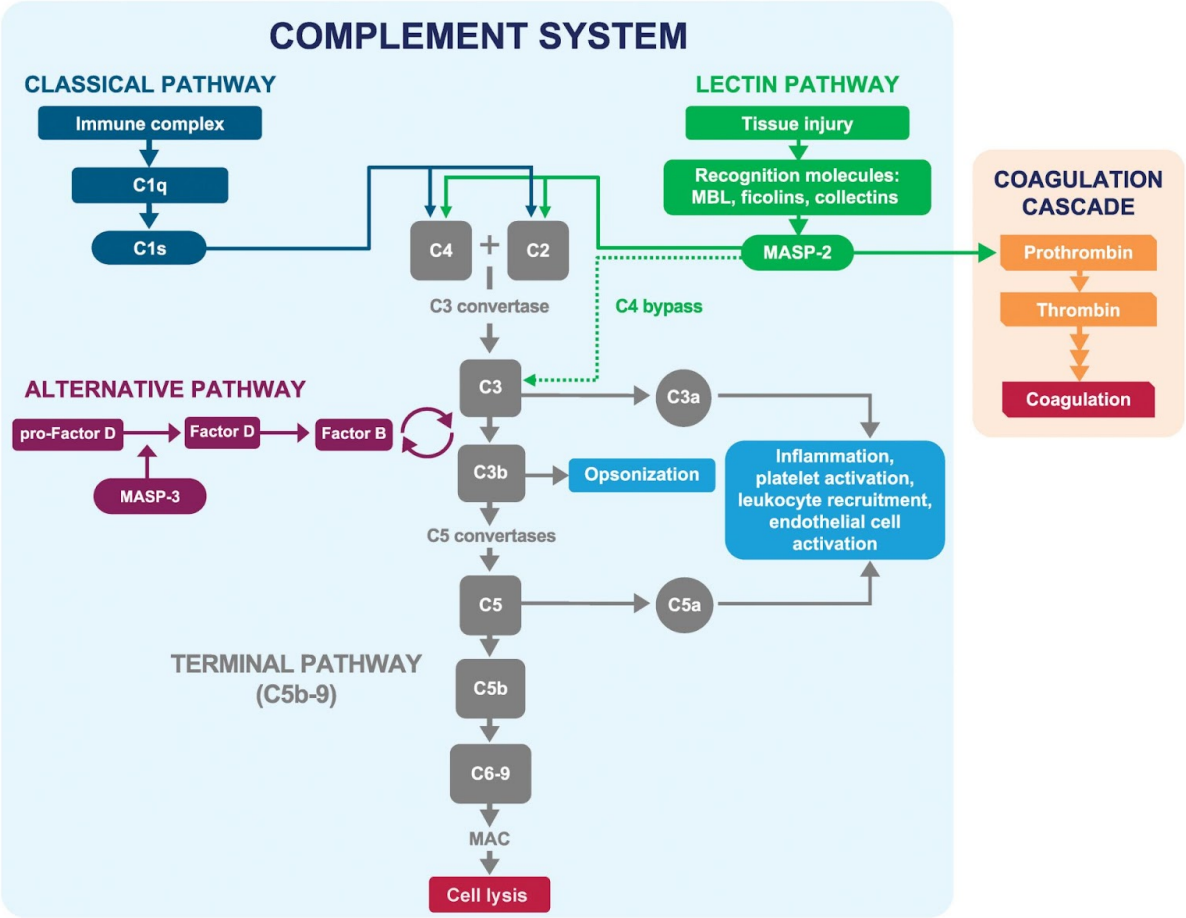
COMPLEMENT MEDIATED TMA (CM-TMA)



7D/ CM-TMA: treatment
🚩Eculizumab - Effective and safe option in pregnancy
⬇️ progression to ESRD, less time on dialysis, successful disease remission
👉A study @NEJM concluded that Eculizumab is safe and effective for pregnant women with PNH
https://pubmed.ncbi.nlm.nih.gov/26352814/

7E/💥 New therapy: Ravulizumab
📍Approved for CM-TMA
📍Longer t1/2 (52 days)
📍More than 10 times greater affinity for neonatal Fc receptor; higher uptake in breast milk
📍Not yet recommended in pregnancy - further studies are needed

7F/ 💥Newer drugs in pipeline:
Crovalimab (anti-C5)
Nomacopan (anti-C5)
Pegcetacoplan (anti-C3)
Iptacopan (anti-factor B)
Narsoplimab (mannose binding lectin-associated serine protease 2 [MASP-2]
https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1297352/full



7G/
🚩Treatment of Factor H autoantibodies
🚩PLEX, Eculizumab, prednisone, rituximab, cyclophosphamide

7H/ CM-TMA: outcomes
🧯Maternal: increased risk of preterm delivery, disseminated intravascular coagulation, end stage renal disease (ESRD), stroke, death
🧯Fetal: small for gestational age, low birth weight

8A/ APS associated TMA: Incidence
👉40-50 patients per 100,000
👉Can occur as primary condition in 50% patients or with SLE/ other systemic autoimmune disease
👉TMA associated with APS : 8-31% in primary cases

8B/ APS: pathophysiology
⚡Antiphospholipid antibodies inhibit anticoagulant cascade and fibrinolytic activity → thrombosis

⚡Two hit hypothesis (image below)
⚡Triggers- infection, sepsis, surgery, smoking, hormonal change in pregnancy
⚡NET(neutrophil extracellular traps) ⬆️ thrombosis

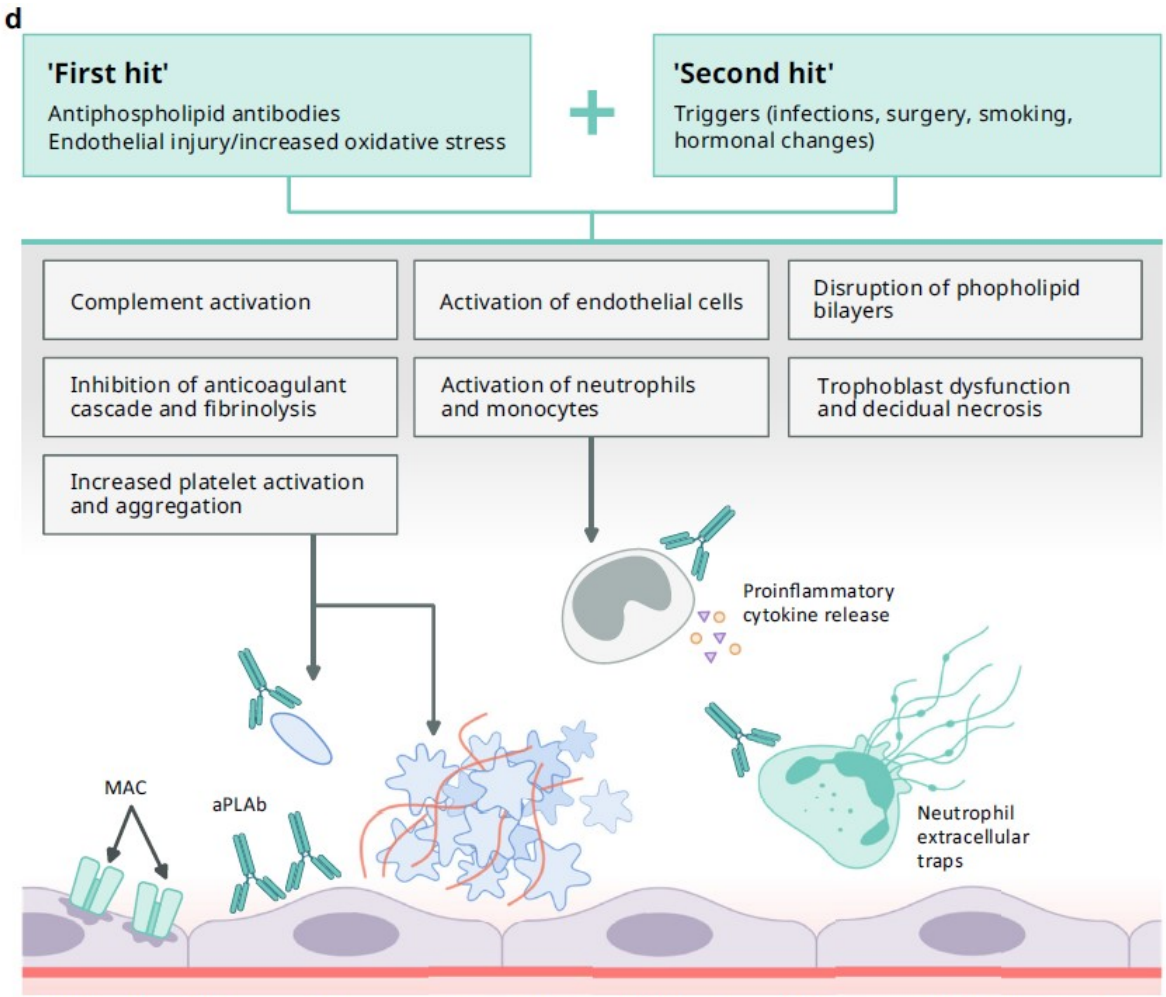
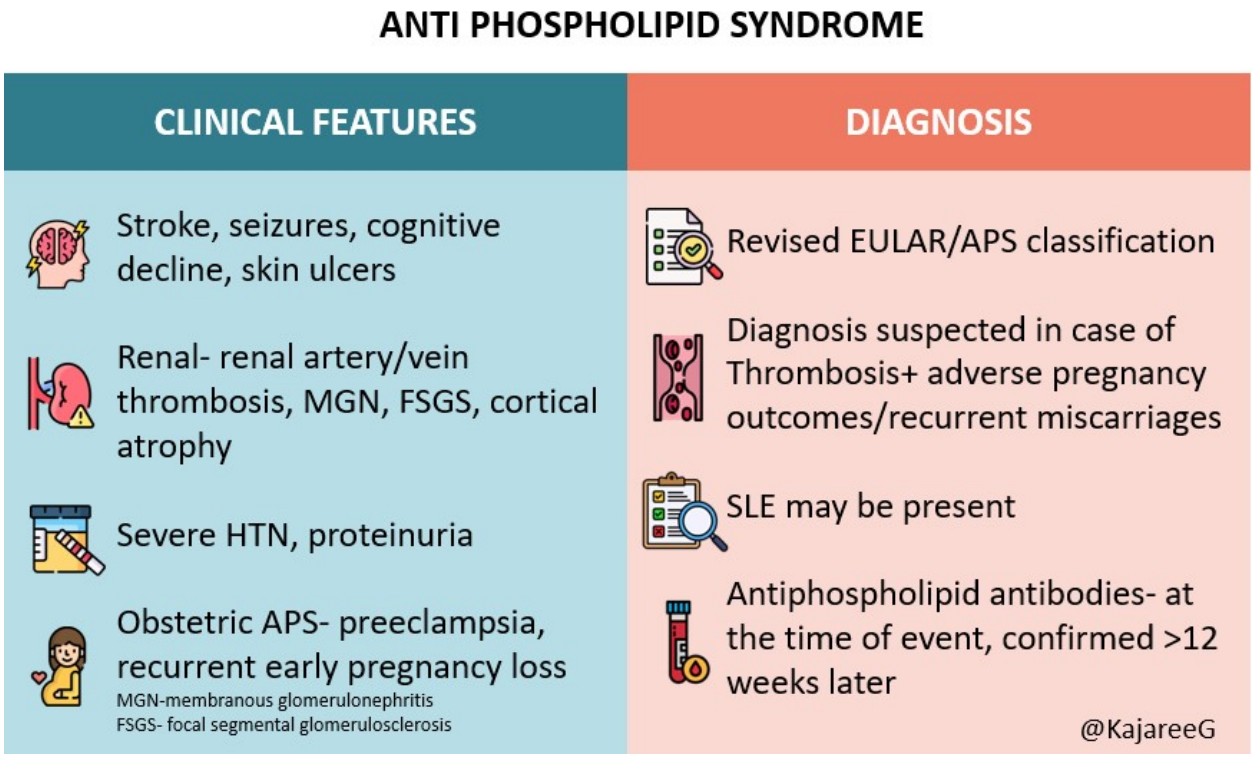
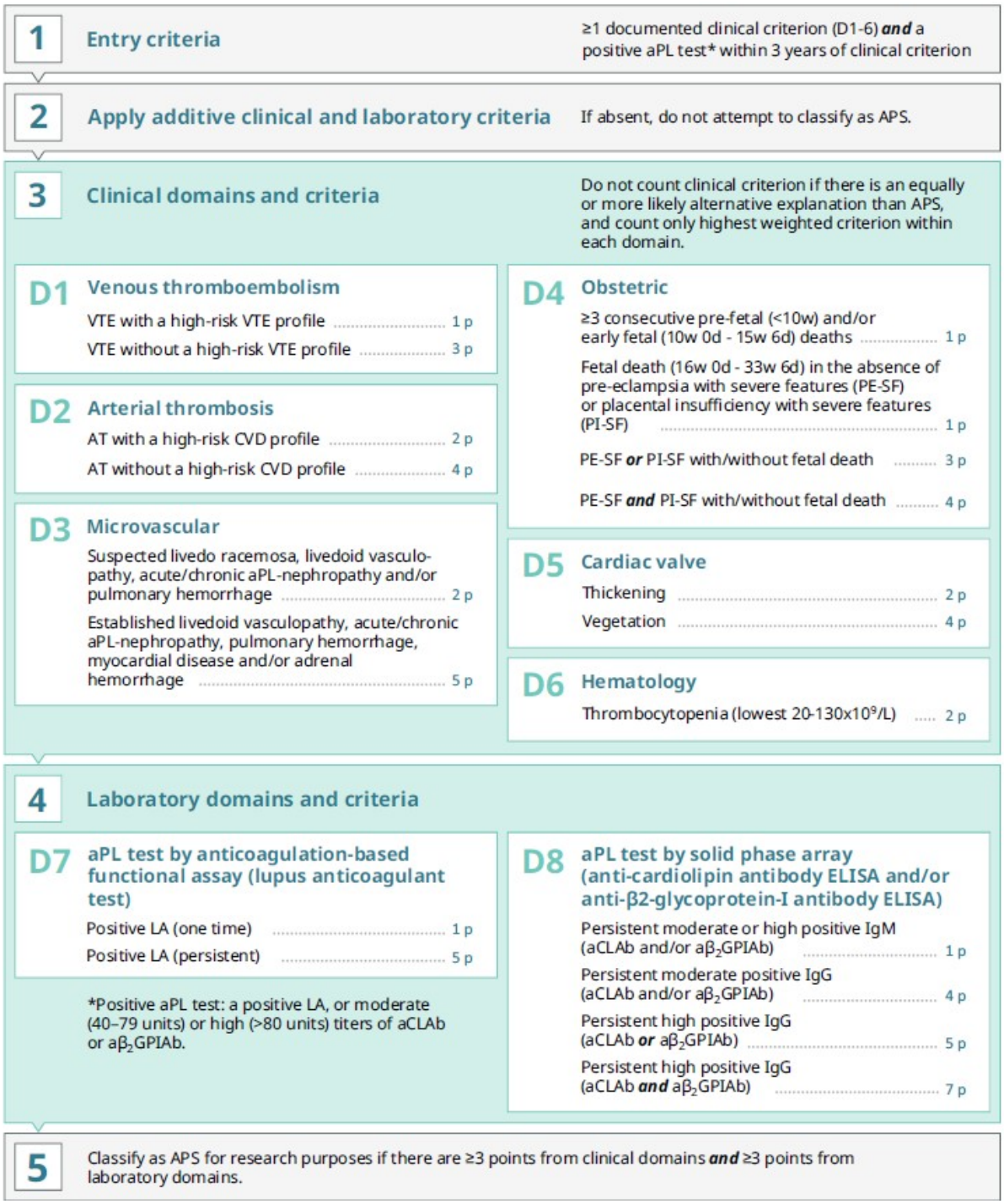


Figure 1. (Continued) (d) Pathogenic mechanisms contributing to Antiphospholipid syndrome (APS) associated TMA. In the "two-hit" model of APS, a trigger event is required to cause manifestations of the disease in patients with preexisting aPL antibodies. Multiple mechanisms contribute to the proinflammatory and procoagulant state that drives pregnancy morbidity in APS syndrome associated TMA. aPLAb, antiphospholipid antibodies.

8C/ APS
📍The clinical features and diagnosis of APS has been summarized in the infographic below:



8D/ ▶ Let's check out the revised ACR/EULAR classification criteria for diagnosis of APS
Image source: https://www.kireports.org/article/S2468-0249(24)01739-X/pdf



8E/ APS:treatment

- Non pregnant patients- warfarin is preferred; aspirin added if there is history of arterial thrombosis
- In pregnancy, low molecular weight heparin (LMWH) is used
- Prophylactic LMWH + aspirin in patients with positive laboratory criteria of APS
- HCQ in SLE

8F/ 💥Catastrophic APS: treatment
👉Anticoagulation + high dose glucocorticoids + PLEX + IVIG
👉In refractory cases - trial of Rituximab/ Eculizumab

8G/💥 APS: Newer therapies
💥TNFα blockers Adalimumab/ Certolizumab - A series on 18 patients revealed that the combination of LMWH + low dose aspirin + TNF-α blockers is a promising treatment option for refractory obstetric APS cases
https://pubmed.ncbi.nlm.nih.gov/30824278/

8H/ 👀Let's check out a review on obstetric APS in @JClinMed, which gives a nice summary on the suggested therapeutic schedules in patients with obstetric APS
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8836886/

Table 5. Suggested therapeutic schedules for OAPS patients.

Gold Standard therapy in spontaneous pregnancy loss: recurrent miscarriage/fetal loss	LMWH 0.4–06 mg/kg/day ("prophylactic" dose) since the positive pregnancy test combined with preconception daily LDA at least one month before starting attempts for a new pregnancy.
Gold Standard Therapy in assisted reproductive techniques (ART)	LMWH 0.4–0.6 mg/kg/day since estrogens are started in the substituted cycle (or 14 days prior to the transfer, if not), combined with preconception LDA, at least one month before starting ART
Women with a previous history of thrombotic APS or thrombosis that appeared during pregnancy	LMWH 1 mg/kg/12 h since the thrombotic event, combined with LDA.
Presence of severe thrombocytopenia (less than 20,000 platelets) or presence of mild-moderate bleeding	Stop LDA LMWH 0.2 mg/kg/day in the case of OAPS LMWH 1 mg/kg/day in thrombotic APS Monitor total platelet count Monitor anti-factor Xa activity
Presence of mild-moderate renal failure (GFR 15–45 mL/min)	Reduce the LMWH dose that was administered and discontinue aspirin. Monitor anti-factor Xa activity monthly
Presence of extreme weights (less than 40 kg or greater than 120 Kg)	LMWH 0.2 to 0.8 mg/kg/day (prophylactic dose adjusted to body weight), since positive pregnancy test combined with preconception LD., Monitoring anti-factor Xa activity monthly.

APS: antiphospholipid syndrome; ART: assisted reproductive techniques; GFR: glomerular filtration rate; LDA: low-dose aspirin; LMWH: low molecular weight heparin; OAPS: obstetric antiphospholipid syndrome.

8I/ 🚨APS:outcomes
🚨Maternal: recurrent miscarriages (in 10-15% of women with APS), higher risk of venous thromboembolism and ischemic cerebrovascular disease

🚨High titers of anticardiolipin antibodies and prior fetal loss - 80% risk of future pregnancy loss

9/💥 Summary:
The wonderful infographic below provides the diagnosis and treatment of four major causes of p-TMA from the review
https://www.kireports.org/article/S2468-0249(24)01739-X/pdf

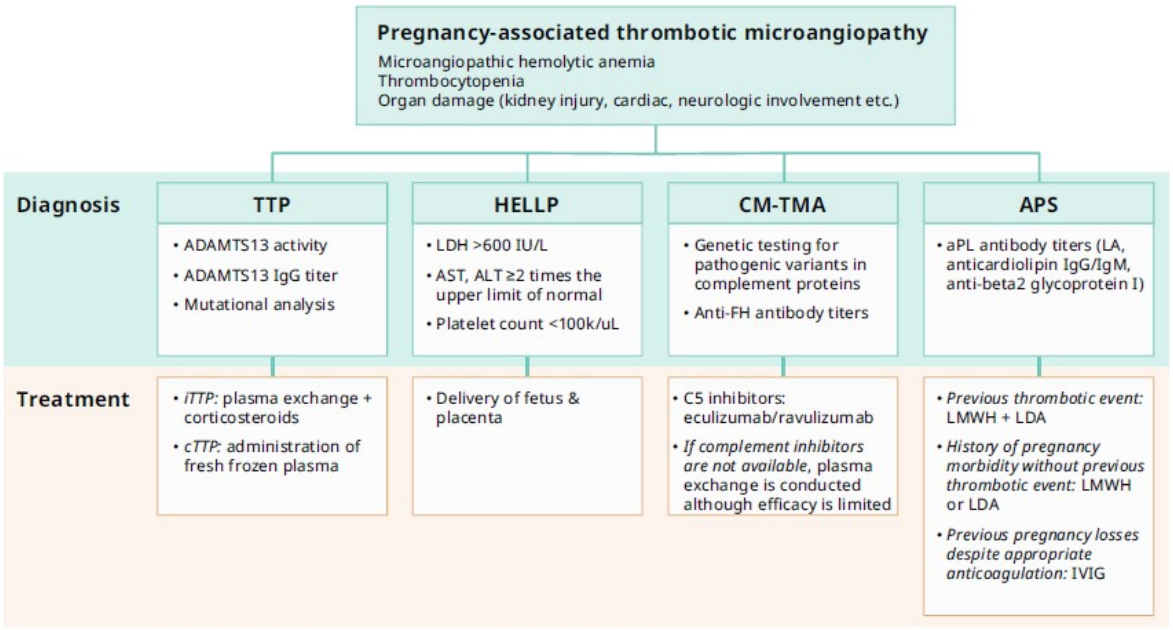
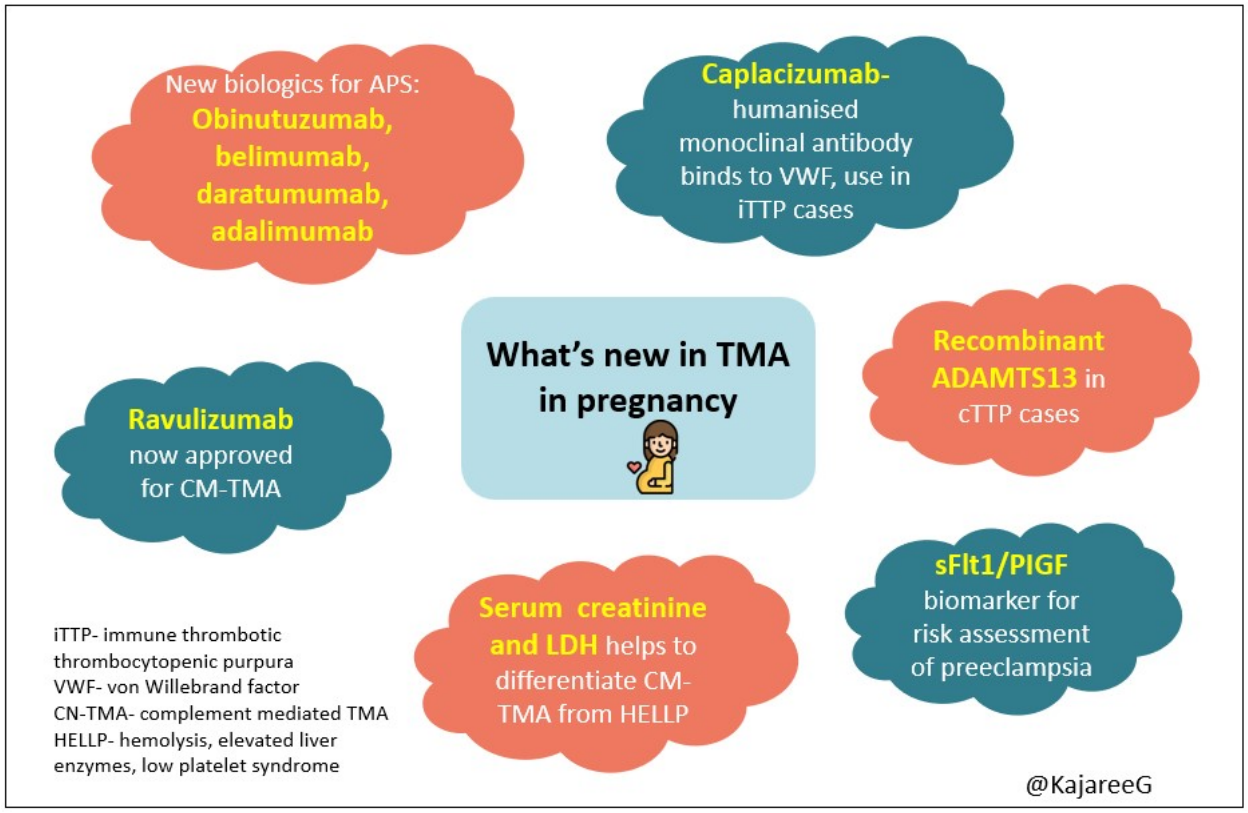


Figure 2. Diagnosis and treatment by type of pregnancy-associated TMA. ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aPL, antiphospholipid; APS, antiphospholipid syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CM-TMA, complement-mediated thrombotic microangiopathy; cTTP, congenital TTP; FH, factor H; HELLP, Hemolysis, Elevated Liver enzymes, Low Platelet count syndrome; IVIG, intravenous immunoglobulin; iTTP, immune TTP; LA, lupus anticoagulant; LDA, low-dose aspirin; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin; TTP, thrombotic thrombocytopenic purpura.

10/ 👀What's new in TMA in pregnancy?
👉Let's check out the summary slide from the review



11/ Conclusion:

▶ p-TMA is a challenging diagnosis

▶ TTP, HELLP, CM-TMA and APS are the four most common etiologies with overlapping features

▶ Thorough clinical history, prompt laboratory data and early identification of patterns of injury help to ⏬ maternal and fetal morbidity

12/ This has been a tweetorial by @KajareeG from #NephEdC 2024 Pod 1 **Filtrate Firebolts**🔥⚡ on behalf of @KIreports and @ISNKidneycare. Special thanks to @sophia_kidney @NephroSeeker @MChanMD and @brian_rifkin for their help and feedback!