THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Pre-Eclampsia and its Impersonators

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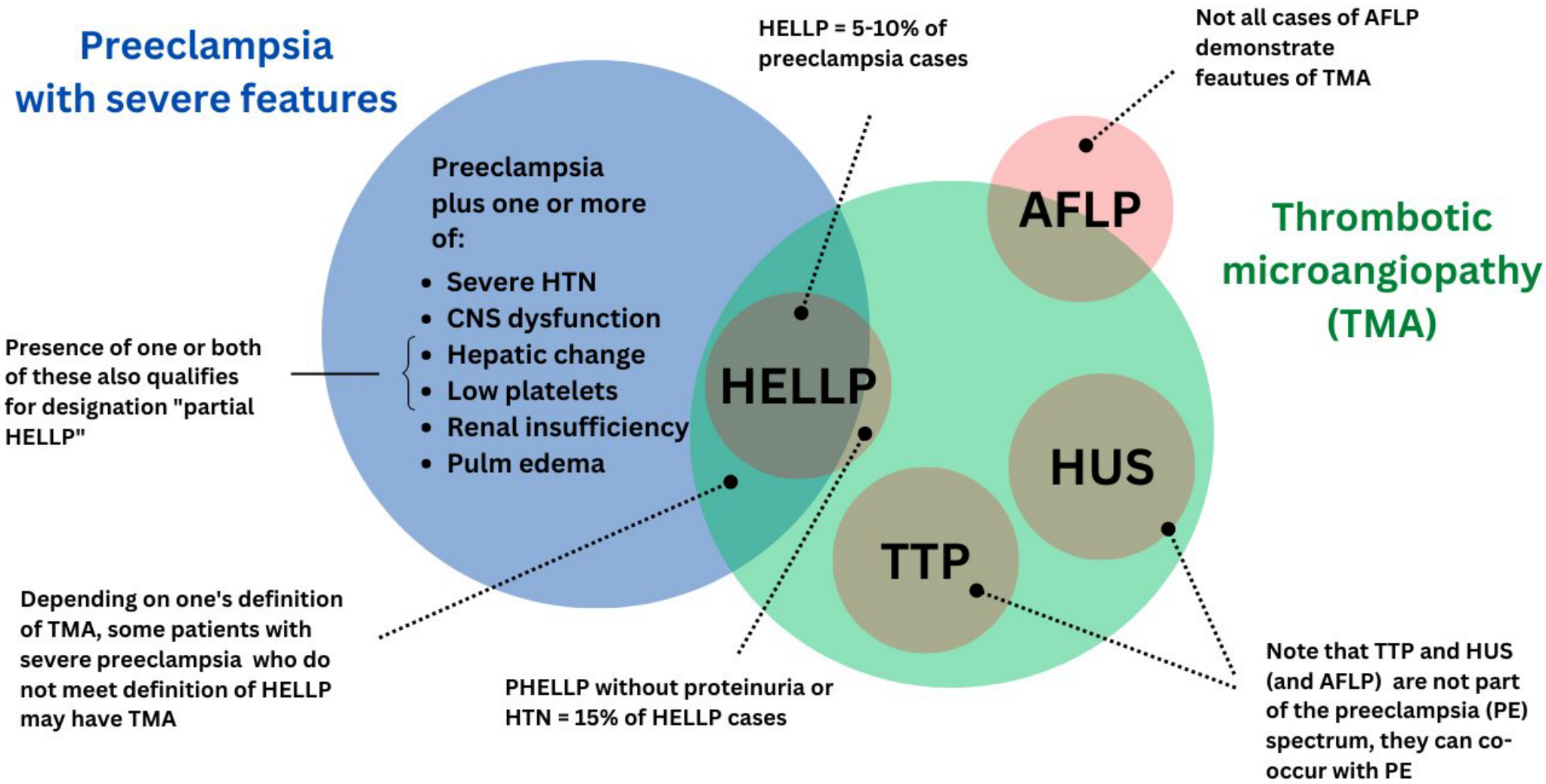
Disclosures

I have no conflicts of interest to declare.

Learning Objectives

- Describe clinical features and diagnosis of pre-eclampsia and its impersonators.
- Improve ability to identify a leading diagnosis in the setting of clinical uncertainty.
- Improve ability to work up multiple clinical entities at once when diagnosis is uncertain.
- Avoid arriving at premature diagnosis of pre-eclampsia.

Severe Preeclampsia vs. TMA in Pregnancy

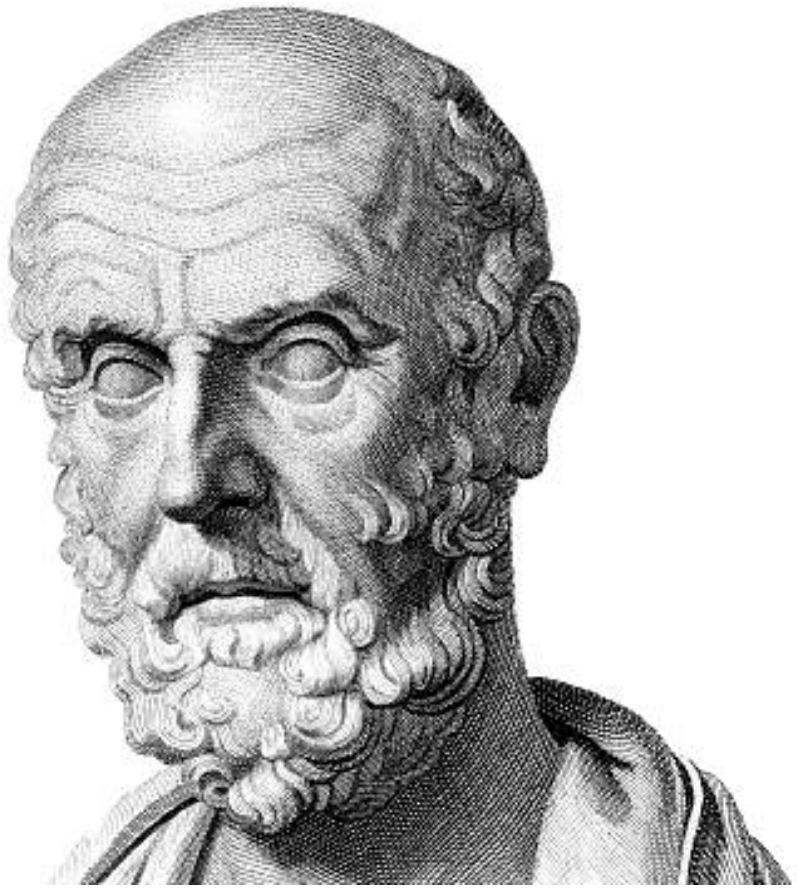


AFLP: acute fatty liver of pregnancy; TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic uremic syndrome

"In medicine, it is prudent always to consider the diagnosis that is likely, as well as the diagnosis that is lethal."

-Dennis Gingrich, MD, FAAFP
c.2013

Pre-eclampsia: “The Disease of Theories”



- 400BC: Hippocrates suggests a “headache accompanied by heaviness [swelling] and convulsions” as being of serious significance in pregnancy
- 1700s: Boissier des Sauvages coins term “eclampsia,” meaning “lightning” in reference to sudden onset of seizures in pregnancy
- 1800: Prodrome characterized: headache, loss of vision, abdominal pain, upper-body edema > ***pre*-eclampsia**
- 1840: Proteinuria is discovered as hallmark of pre-eclampsia
- 1896: Sphygmomanometer invented– pre-eclampsia recognized as hypertensive disorder of pregnancy

A Brief History of Pre-eclampsia

A STUDY OF FIVE HUNDRED CONSECUTIVE CASES OF PRE-ECLAMPSIA*

By Frederick C. Irving, M.D., F.A.C.S.

Boston, Mass.

THE object of this paper is to review in an unselected group of clinic cases the results of a definite and uniform policy of treatment. For this purpose were chosen the pre-eclamptic registered patients delivered in the Boston Lying-in Hospital between April 21, 1935, and January 1, 1937. Of these 500 patients 397, or 79.4 per cent, were classified as having a mild type of pre-eclampsia; that is, hypertension of moderate degree with no more than a slight trace of albumin in the urine. The other 103, or 20.6 per cent, were of the severe type, having marked or increasing hypertension and albuminuria. Included in the entire group were 16 cases which were considered as primarily hypertensive since they exhibited marked and persistent elevation of blood pressure with little if any albuminuria and no evidences of renal failure. Three patients were diagnosed as nephritics, as they presented signs of diminished kidney function persisting over a long period. The patients were equally divided into 252 primiparæ and 248 multiparæ. Seventy of the multiparæ, or 27.8 per cent, had had pre-eclampsia in a previous pregnancy. There were 16 pairs of twins, a frequency of 1 in 31.2, as contrasted with the normal expectancy of 1 in 87. Eight of the 500 pre-eclamptic patients, or 1.6 per cent, developed premature separation of the placenta. In view of the recognized relationship between these two conditions this low incidence is both surprising and gratifying.

Table I shows the frequency of the leading signs and symptoms. It will be noted that 7 of every 10 pre-eclamptics developed œdema. It

Table I.

Signs and Symptoms

	Number	Percentage
Œdema	358	71.6
Headache	209	41.8
Vomiting	137	27.4
Visual disturbances	135	27.0

was also found that the average gain in weight was 0.74 of a pound per week for the period of observation, as compared with the average gain of 0.5 of a pound generally accepted for the normal woman in pregnancy.

Routine blood chemical determinations were made in 452 cases. Chart 1 shows that abnormal findings were obtained in only 14.1 per cent, thus indicating that considerable laboratory work was wasted in this type of case. Our experience suggests that the urea and uric acid content of the blood is seldom elevated unless the non-protein nitrogen exceeds the normal limits, and that the determination of even this factor is seldom necessary unless there is reason to suspect impairment of kidney function. A similar statement may be made regarding the urea-clearance test. This test was performed in only 38 cases where restricted kidney function was suspected and showed a diminished clearance in 28.9 per cent. On the other hand, ophthalmoscopic examination of the eye grounds revealed sclerosis of the retinal vessels to some degree in 52.6 per cent. This condition was found in 73.3 per cent of the severe pre-eclamptics examined and in 39.1 per cent of those of mild degree. The special examination was made by our Assistant Ophthalmologist, Dr. W. R. Beetham, in 190 cases. The results indicate the close relationship between pre-eclampsia and the vascular system.[1]

* From the Department of Obstetrics, Harvard Medical School and the Boston Lying-in Hospital.

Read at the Sixty-ninth Annual Meeting, Canadian Medical Association, June 24, 1938.

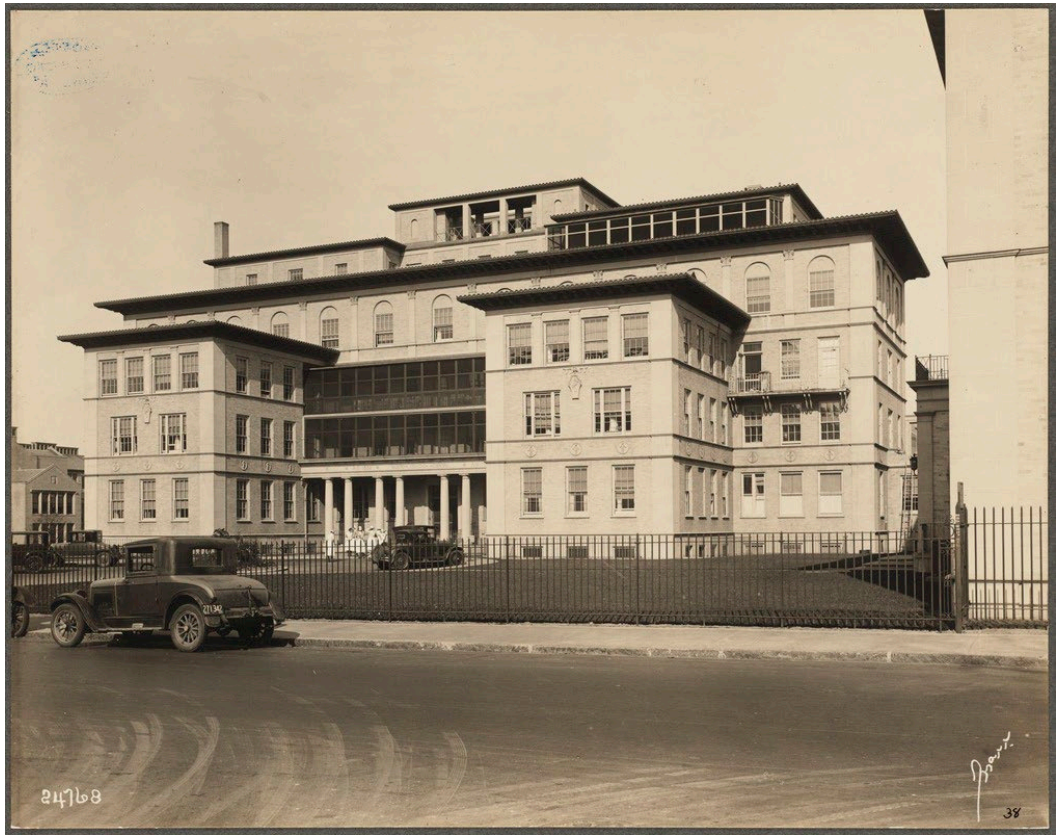
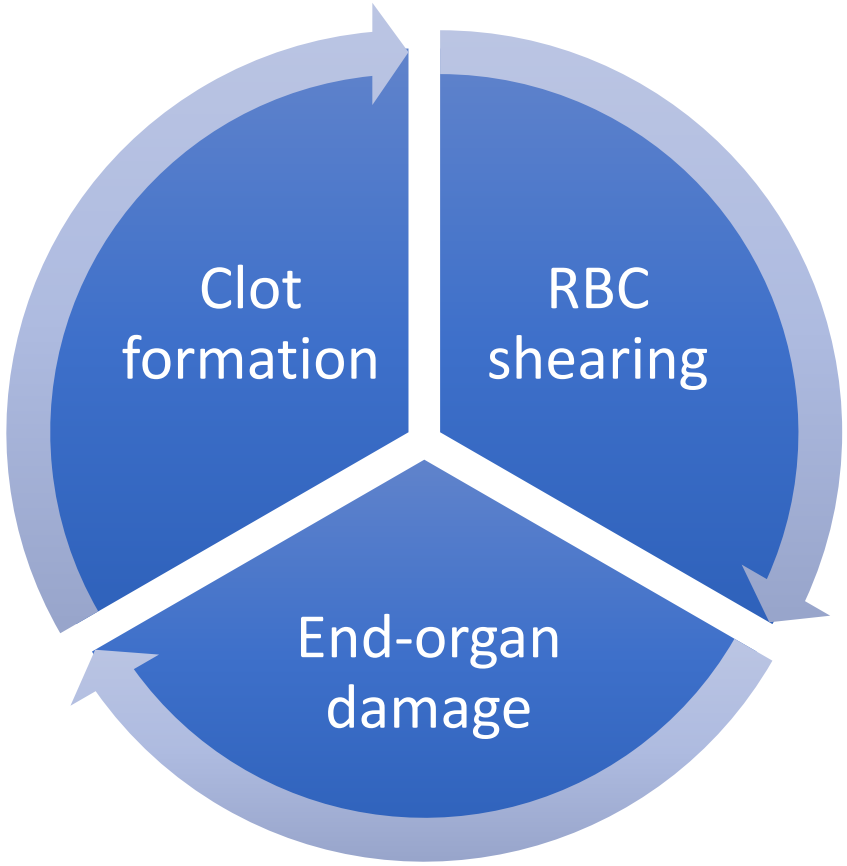
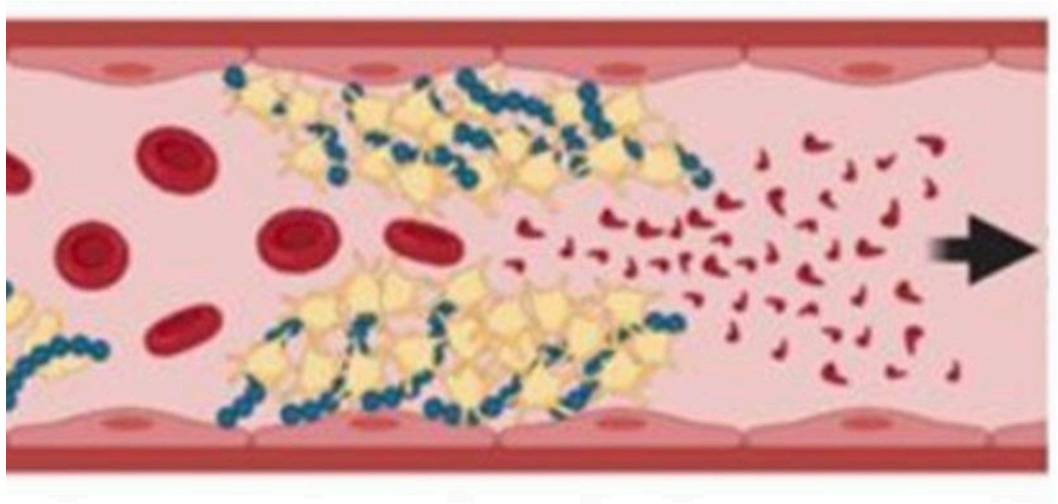


Table 1
Diagnostic criteria for severe features of preeclampsia over time (American College of Obstetricians and Gynecologists).

Severe Feature	Before 2002	2002–2013	2013-Present
Blood pressure	≥160 mmHg systolic or ≥ 110 mmHg diastolic	≥160 mmHg systolic or ≥110 mmHg diastolic	≥160 mmHg systolic or ≥110 mmHg diastolic
Kidney	Proteinuria ≥5 g in 24hr	Proteinuria ≥ 5 g in 24hr	Not applicable
	Oliguria < 400 ml in 24hr	Oliguria < 500 ml in 24hr	Not applicable
	Not applicable	Not applicable	Creatinine > 1.1 mg/dl or 2× baseline
Brain/Eyes	Cerebral or visual disturbances	Cerebral or visual disturbances	Cerebral or visual disturbances
Lungs	Pulmonary edema or cyanosis	Pulmonary edema or cyanosis	Pulmonary edema
Liver	Not applicable	Impairment of liver function	Liver enzymes ≥ 2x normal
	Not applicable	Severe or persistent abdominal pain in epigastric area or right upper quadrant	Severe or persistent abdominal pain in epigastric area or right upper quadrant
Placenta/Fetus	Not applicable	Fetal growth restriction	Not applicable
Platelet count	Not applicable	< 100,000/μl	< 100,000/μl

Thrombotic Microangiopathies

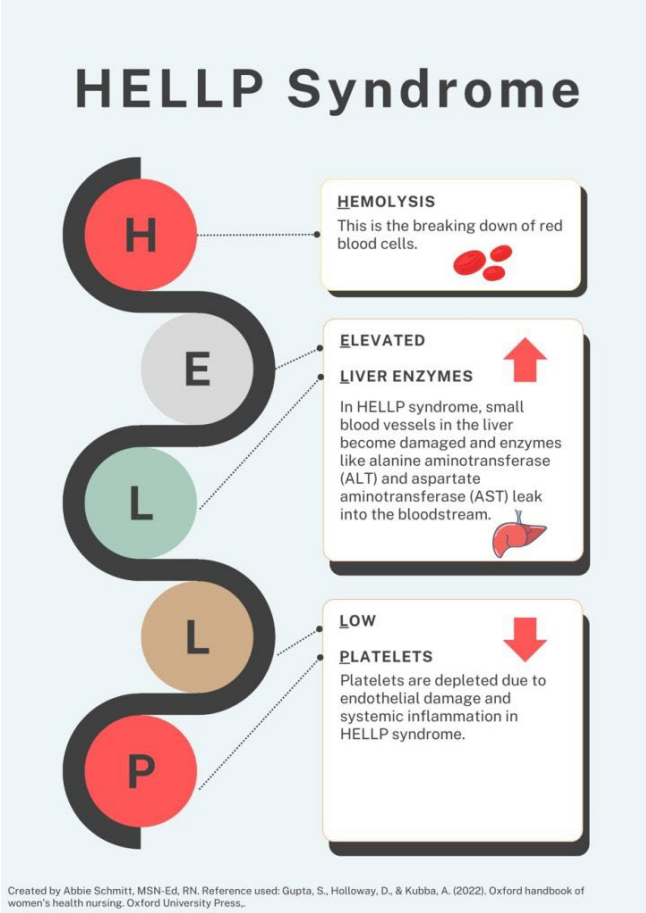




HELLP

A continuation of pre-eclampsia or a separate entity?

- 15-20% of HELLP is diagnosed in the absence of hypertension or proteinuria
- Diagnostic triad:
  - **Hemolysis**
    - Abnormal peripheral smear (schistocytes)
    - Total bilirubin >1.2mg/dL
    - LDH >600 U/L
  - Elevated liver enzymes (>2x upper limit of normal)
  - **Low platelets**
    - <100K/microL
- Can also see other features of pre-eclampsia (**kidney injury**, neurologic sequelae, pulmonary edema)

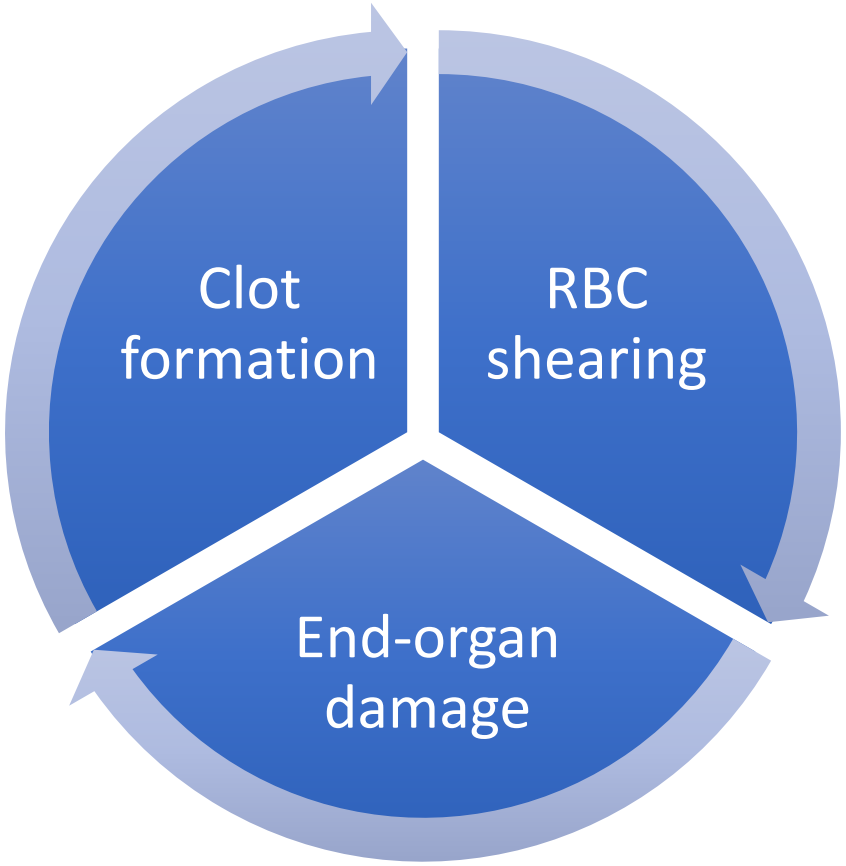


HELLP

- Treatment: Delivery
  - Not necessarily Cesarean
- Natural History: resolution within 48-72h of delivery

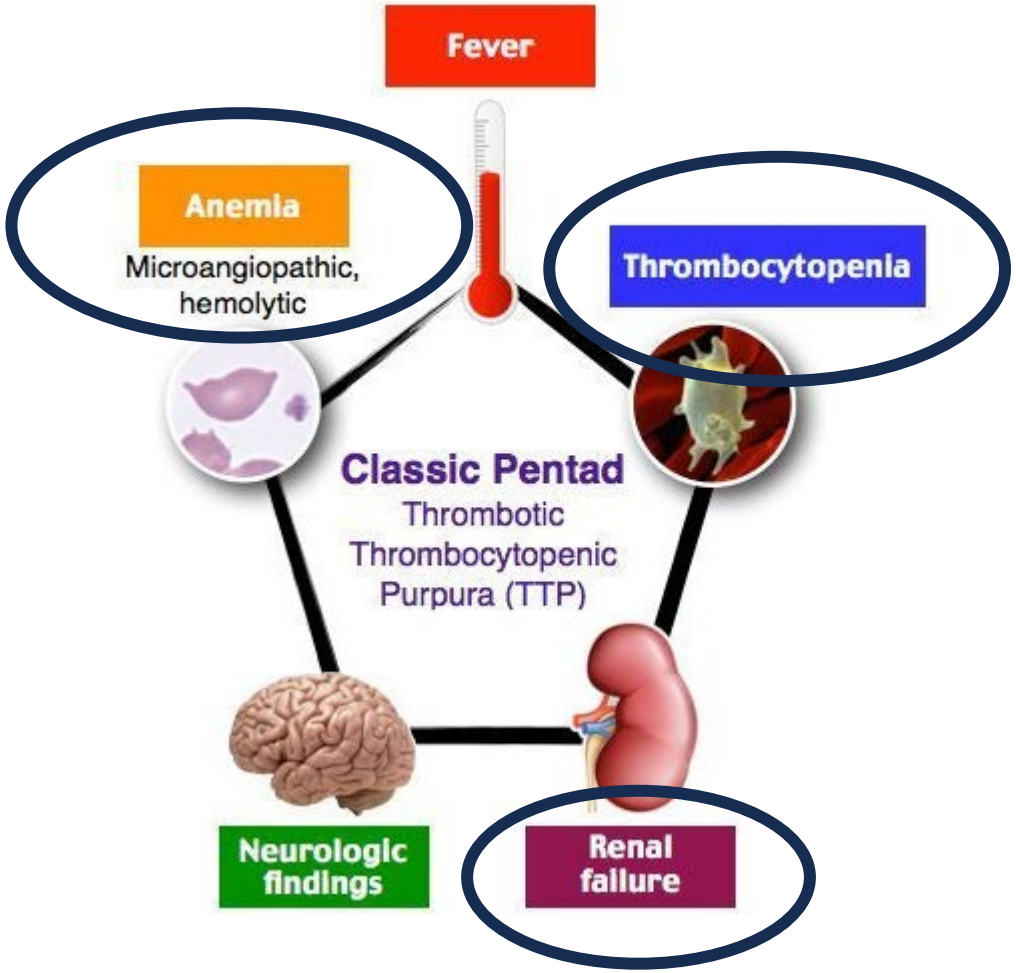
When you hear hoofbeats,
sometimes it's a zebra

Thrombotic Microangiopathies

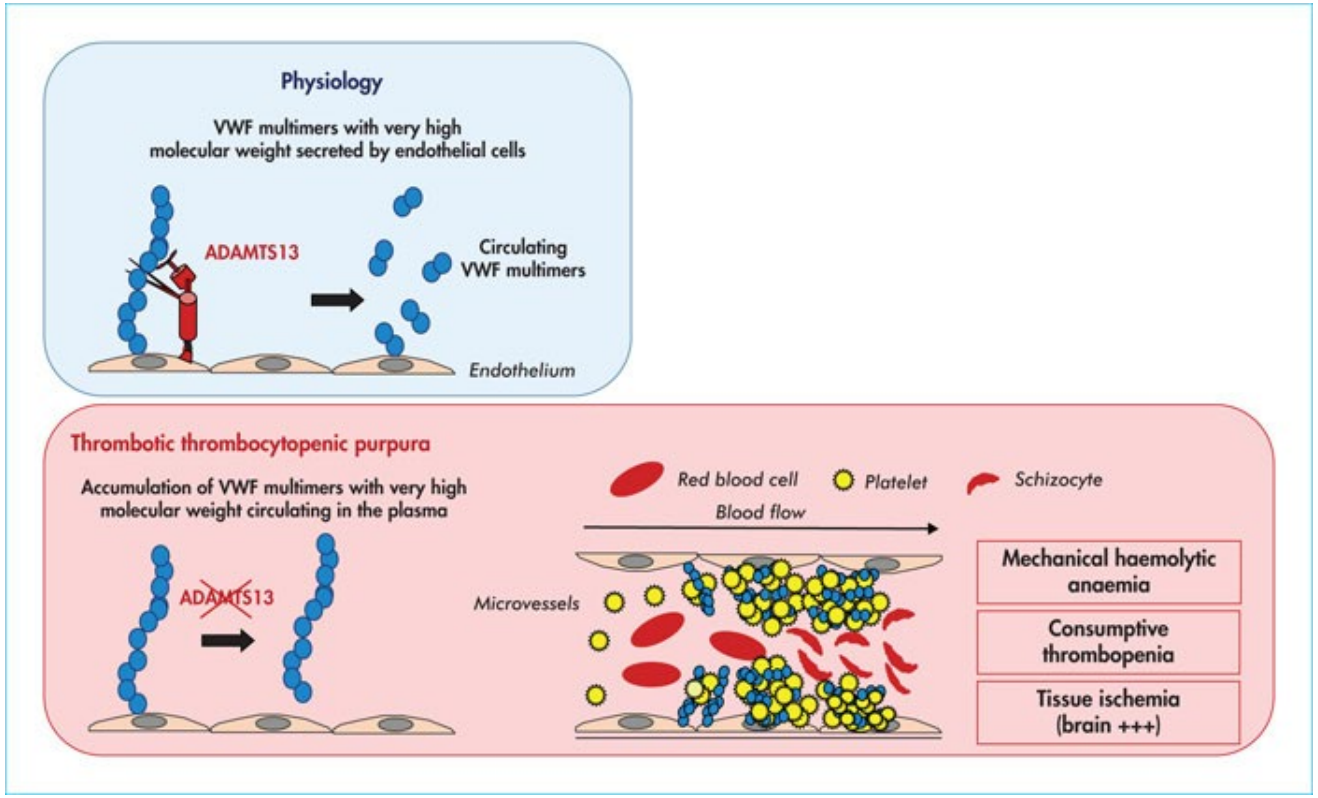


Impersonator #1: Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic Thrombocytopenic Purpura



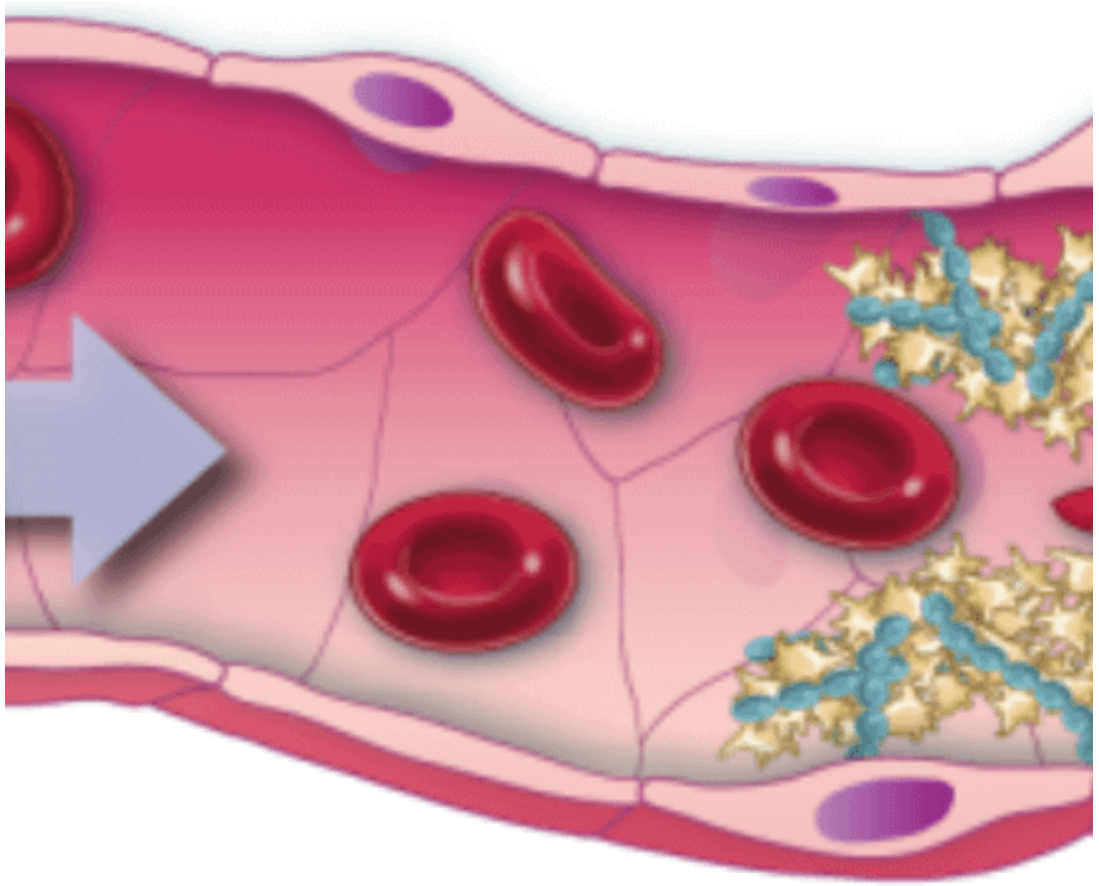
Thrombotic Thrombocytopenic Purpura



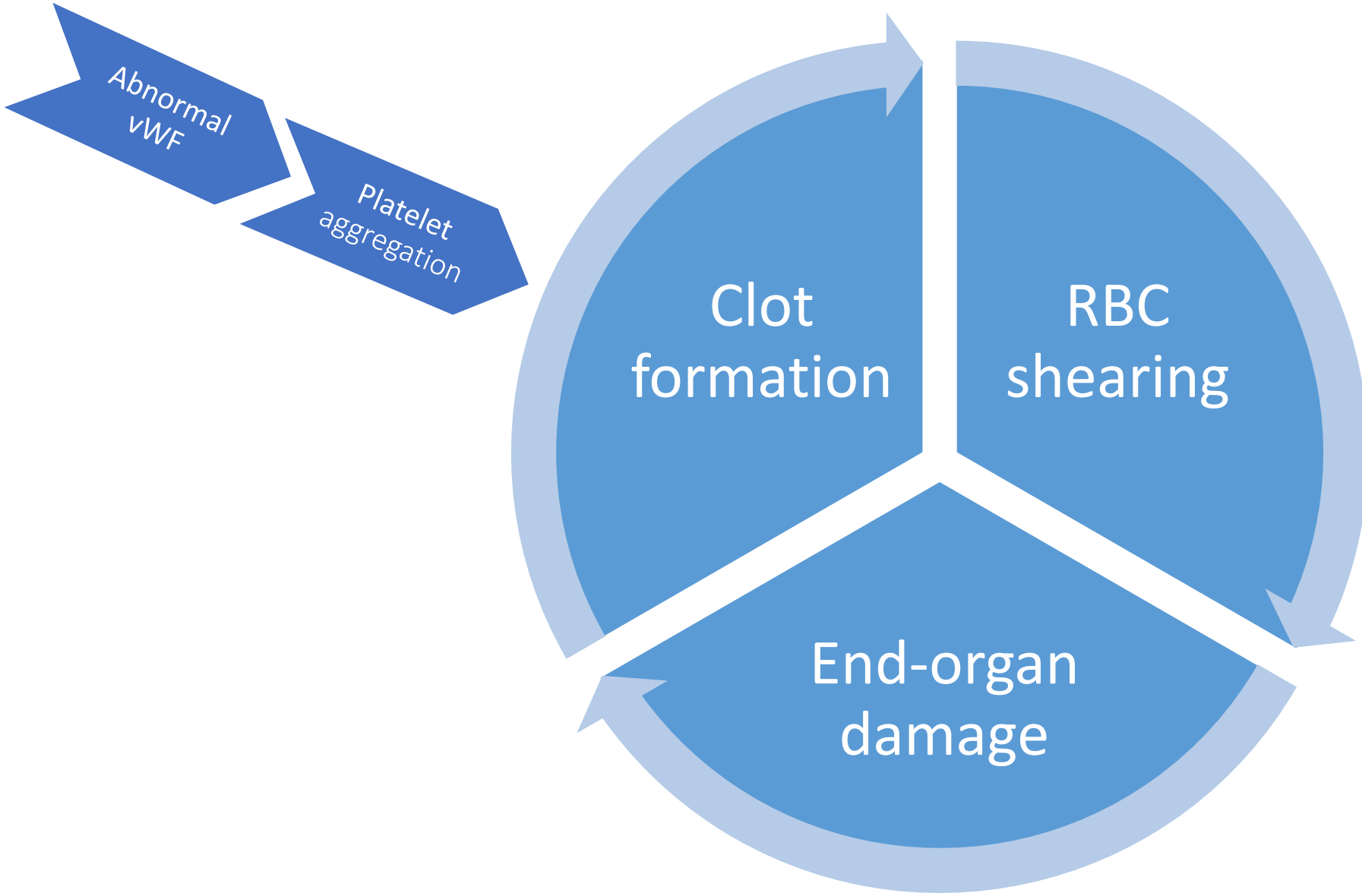
- Normal physiology:
  - vWF released in “ultra-long” form (ULvWF) in response to blood vessel injury
  - ADAMTS-13 cleaves ULvWF to functional vWF units
  - Platelet aggregates form to “plug” injured endothelium

- TTP:
  - Antibodies against ADAMTS-13 prevent cleavage of ULvWF
  - ULvWF forms large platelet/vWF aggregates
  - Platelets are used up in abnormal clot formation (consumptive **thrombocytopenia**)
  - RBCs shear (mechanical **hemolysis**)
  - Microvascular thrombi affect end organs (**kidney injury**)

Thrombotic Thrombocytopenic Purpura



- Diagnostic considerations:
  - Marked thrombocytopenia in first half of pregnancy (<70K)
  - Hemolytic anemia and **profound thrombocytopenia in second half of pregnancy or postpartum**
  - Can be associated with fever, AMS, AKI
  - **AKI does not tend to be severe (sCr ~2.0).**
- Diagnosis:
  - **ADAMTS-13 activity <10% in setting of anemia and thrombocytopenia**
- Treatment:
  - Plasmapheresis (removes ADAMTS-13 inhibitor)
  - Platelet transfusion can exacerbate underlying disease, increase risk of cardiovascular events, or death
  - If TTP is leading differential, consult Hematology.


Abnormal vWF
Platelet aggregation
Clot formation
RBC shearing
End-organ damage

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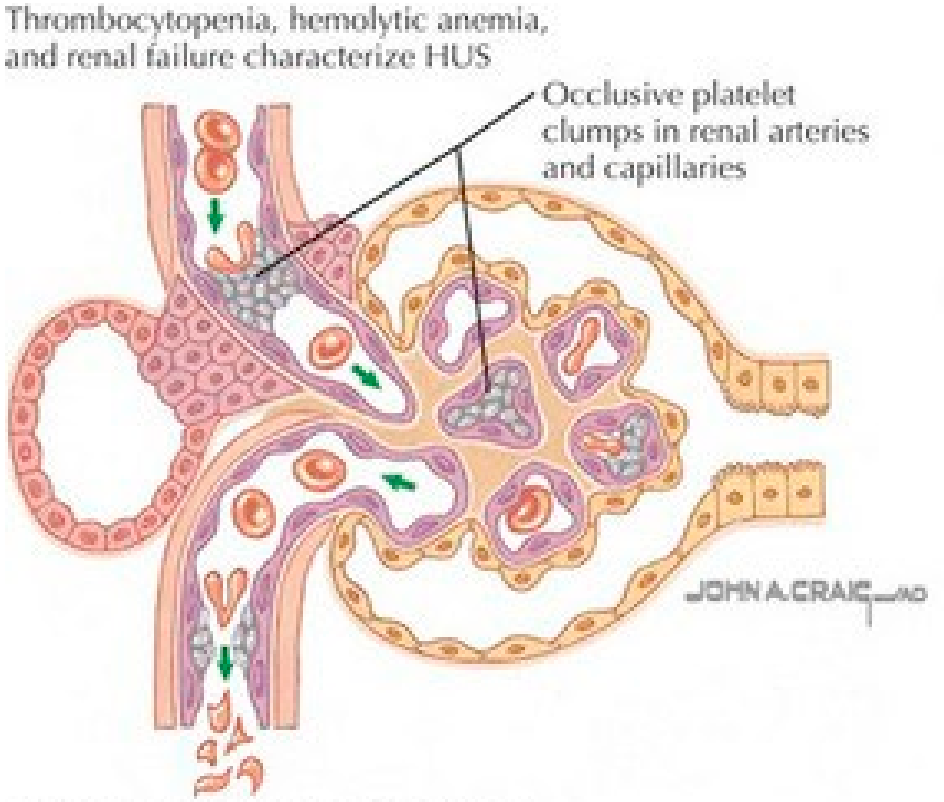
Impersonator #2: Atypical Hemolytic Uremic Syndrome

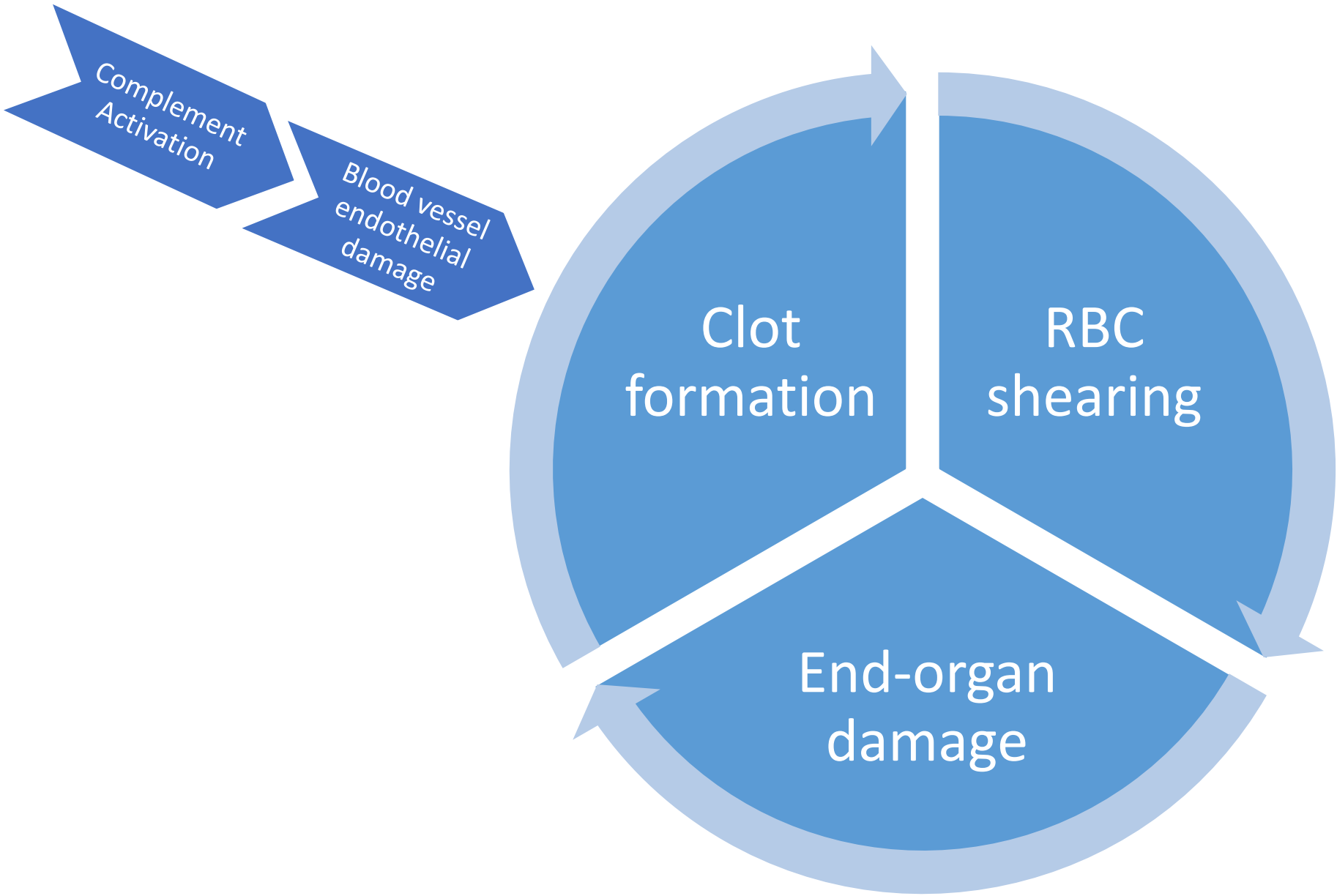
Atypical Hemolytic Uremic Syndrome

- Pathophysiology:
  - Excessive **immune system (complement) activation** leads to build-up of protein "clumps" in vessel walls causing damage
  - Widely-damaged endothelium causes platelet aggregation (**consumptive thrombocytopenia**) and formation of microthrombi
  - Microthrombi cause mechanical **hemolysis**
  - Microthrombi deposit in kidney, causing acute kidney injury (**uremia**)



Atypical Hemolytic Uremic Syndrome

- Diagnostic considerations:
  - Typically preceded by **pre-eclampsia, placental abruption, fetal demise, or postpartum hemorrhage**
  - Consider when microangiopathic hemolytic anemia and thrombocytopenia **<20 weeks gestation OR >48-72h postpartum**
  - **Mean LDH > 2,000 U/L**
  - **Mean serum creatinine > 6 mg/dL**
  - If aHUS is leading differential, involve Hematology and Nephrology.
- Treatment:
  - Complement blockade with eculizumab
- Natural History:
  - Recovery over weeks – months
  - Most patients left with residual renal deficit


Complement Activation
Blood vessel endothelial damage
Clot formation
RBC shearing
End-organ damage

Impersonator #3: Acute Fatty Liver of Pregnancy

Acute Fatty Liver of Pregnancy

- Pathophysiology: Impaired long-chain fatty acid metabolism in fetus leads to fulminant maternal hepatic failure
- Presentation: Non-specific, “unwell”
  - Malaise
  - Anorexia
  - Nausea/vomiting
  - RUQ pain
  - Decreased fetal movement
  - Altered mental status (hepatic encephalopathy)
  - +/- pre-eclampsia/HELLP (40% of cases)

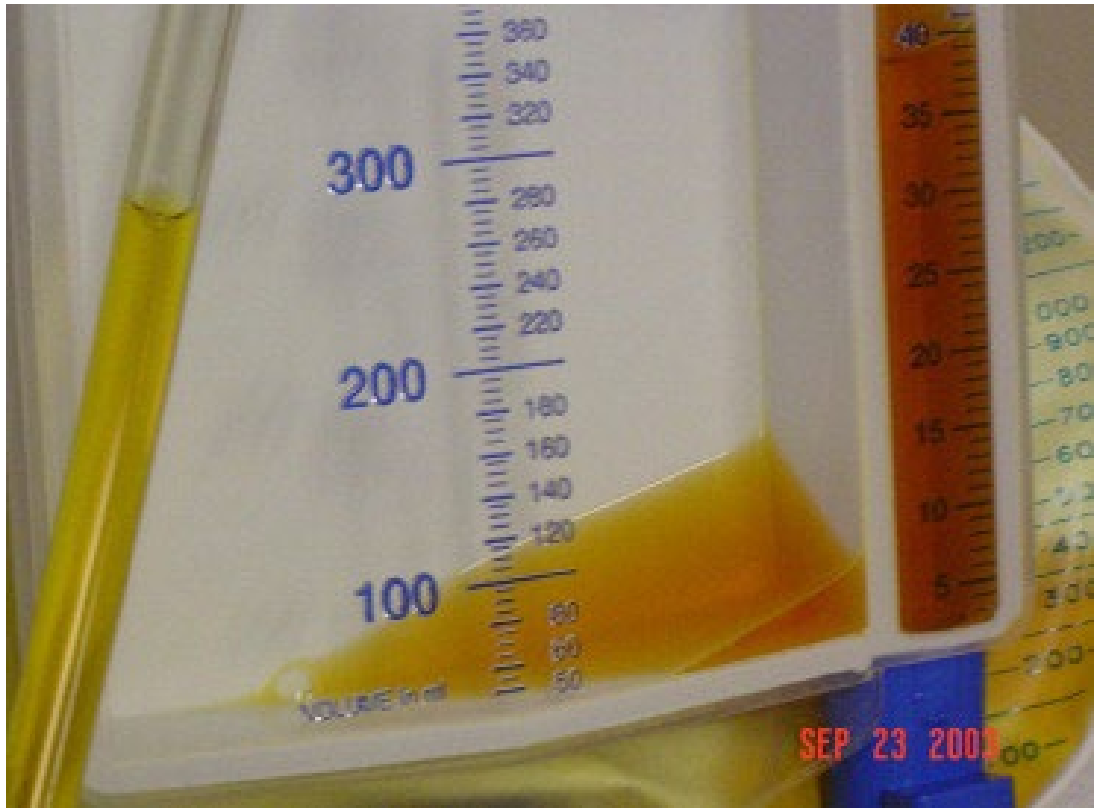


Table 2	Swansea Criteria for the Diagnosis of Acute Fatty Liver of Pregnancy[16]
Six of the features below are required for the diagnosis	
Clinical features	■ Nausea and vomiting ■ Abdominal pain ■ Encephalopathy ← ■ Polyuria or polydipsia
Laboratory features	■ Bilirubin >0.8 mg/dL ■ Hypoglycemia <72 mg/dL !!! ■ WBC >11x10^9/L ■ AST or ALT >42 units/L ← ■ AKI or Cr >1.7 mg/dL ← ■ Coagulopathy or PT >14 sec !!! ■ Ammonia >47 μmol/L ■ Urate >340 μmol/L
Ultrasonographic features	Ascites or echogenic liver
Histologic features	Microvesicular steatosis on liver biopsy

AKI, acute kidney injury; ALT, alanine transaminase; AST, aspartate transaminase; Cr, creatinine; PT, prothrombin time; WBC, white blood cell count.

AFLP: Outcomes

- AFLP characterized by sudden and fulminant maternal and fetal deterioration
- Treatment is delivery
  - Consider Cesarean delivery if induction expected to take >24h
- Maternal mortality ~10%
  - Hemorrhage, liver failure, kidney injury
- Perinatal mortality 13.1%
  - Average age at delivery 34 weeks
- Convalescence is slow, requires multidisciplinary team

Impersonator #4: Systemic Lupus Erythematosus

Systemic Lupus Erythematosus

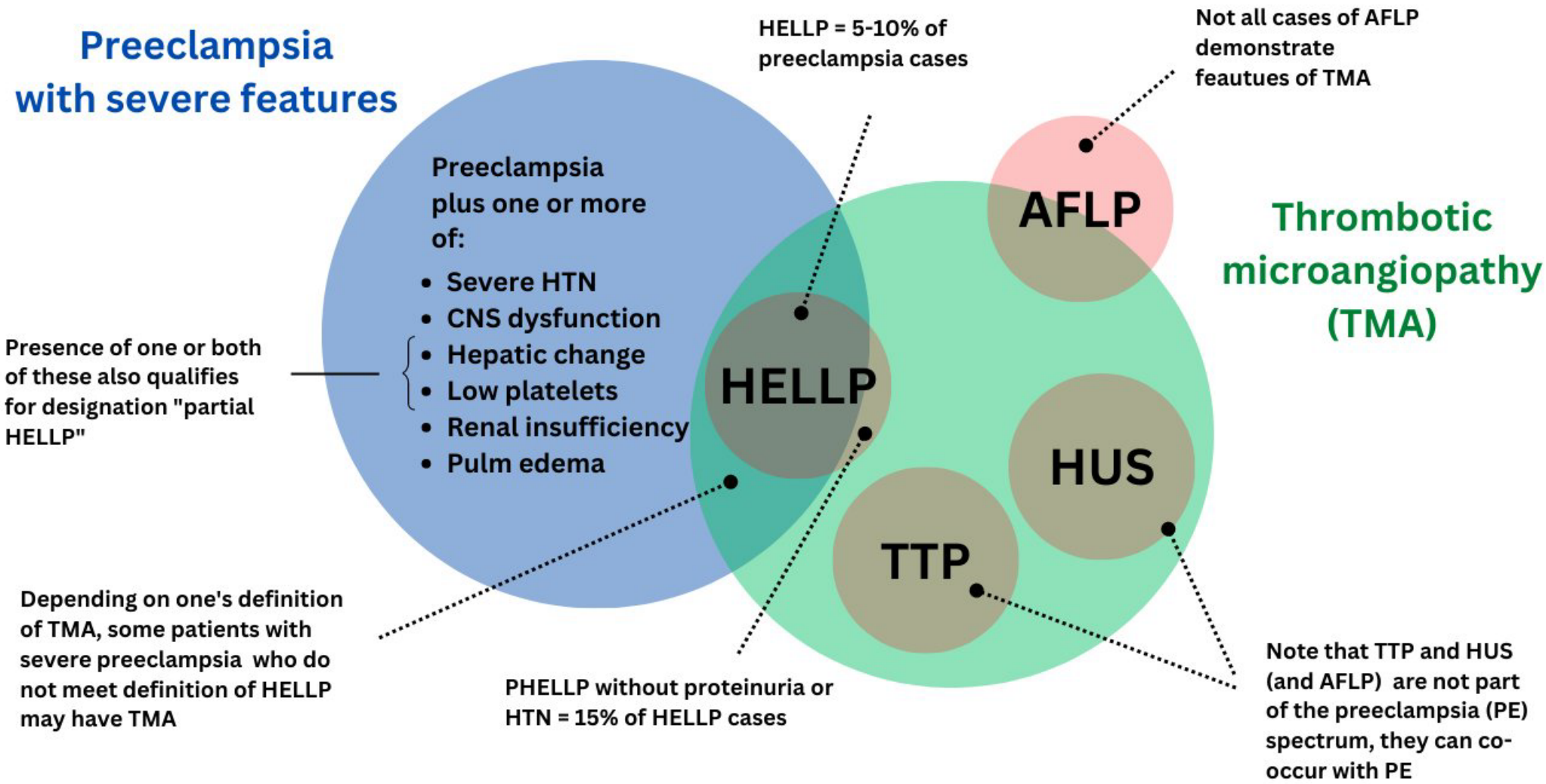
- Pathophysiology: Autoimmune disorder causing antigen-antibody complexes to deposit in capillaries and small vessels
- Presentation:
  - Multi-organ impairment:
    - **Hypertension**
    - Rash
    - Joint pain
    - **Thrombocytopenia (typically >50K)**
    - **Hemolysis**
    - **Renal impairment**
    - Mucocutaneous ulcers
    - Immunologic criteria (anti-dsDNA, anti-Smith, antiphospholipid antibodies, low complement)

Systemic Lupus Erythematosus

- Treatment
  - Steroids
  - Hydroxychloroquine
  - Heparin
- Delivery may not be necessary if SLE is leading diagnosis and improvement is seen with treatment.


PUT IT ALL
TOGETHER

Severe Preeclampsia vs. TMA in Pregnancy



AFLP: acute fatty liver of pregnancy; TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic uremic syndrome

Differentiating the Disorders

	Hemolysis	Thrombocyto-penia	AKI	Natural History	Diagnosis	Treatment
Pre-eclampsia/ HELLP	++ (LDH >600)	++	++	Improves in 48-72h		Delivery
TTP	+++	+++ (<20K)	++ (sCr ~2)	Weeks - months	↓ ADAMTS13	Plasmapheresis
aHUS	+++ (LDH >2,000)	++	+++ (sCr >6)	Weeks-months	↓ Complement	Eculizumab
AFLP	+/-	-	++	Weeks - months	Coagulopathy, ↑ammonia levels, severe elevation in LFTs	Supportive
SLE	+/-	+/-	+/-	Chronic	↓ Complement, ↑ antibody levels	Steroids, hydroxychloroquine, heparin

Take-Aways

- Pre-eclampsia/HELLP are relatively common disorders that may result in hemolysis, low platelets, and organ dysfunction.
- Several other more severe disorders—TTP, aHUS, AFLP, SLE—may mimic pre-eclampsia/HELLP syndrome.
- Symptom severity, degree of lab abnormalities, and failure to improve >72h after delivery are "red flags" that point to potential other causes.
- Workup of multiple conditions may take place simultaneously, allowing arrival at a leading diagnosis, involvement of consultants, and earlier treatment and recovery resulting in lower morbidity.

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Thank you!