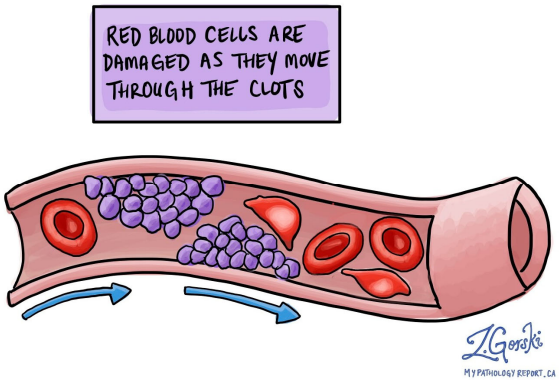
Thrombotic Microangiopathies and you: When to Sound the Alarm

With Miguel Quirch PGY-6 Hematology/Oncology



https://www.mypathologyreport.ca/thrombotic-microangiopathy/

Objectives

1. Understand the pathogenesis behind thrombotic microangiopathies (TMA)
2. Recognize the presentation of TMAs
3. Understand measures to do and NOT to do

Thrombotic Microangiopathy (TMA)

- A type of non-immune microangiopathic hemolytic anemia (MAHA)
- Circulating red blood cells are lysed from microthrombi obstructing flow in blood vessels
- Caused by a variety of conditions and may not always present with MAHA initially

Thrombotic Microangiopathy (TMA)

- Tend to be characterized by :
  - Thrombocytopenia
  - Microangiopathic hemolytic anemia
  - Organ dysfunction due to ischemic injury
- Associated with high mortality if not appropriately treated
- Associated with syndromes that tend to recur

TMA - Subtypes

Category	Defining Characteristic
Disseminated intravascular coagulation (DIC)	Coagulation abnormality with elevated INR and aPTT
Thrombotic thrombocytopenic purpura (TTP)	ADAMTS13 <5%-10%; autoantibody inhibitor of ADAMTS13 (unless one of the rare congenital forms, with no inhibitor)
Atypical hemolytic uremic syndrome (aHUS)	ADAMTS13 >5%-10% (exact cut-off as specified by the laboratory and assay technique employed); associated with a recognized complement-activating condition in two-thirds of cases; congenital mutation in complement system recognized in 70% of cases
Shiga toxin–producing *E. coli* HUS (STEC-HUS)	Stool sample or rectal swab positive for *E. coli*–producing Shiga toxin by culture and/or PCR (both should be performed)

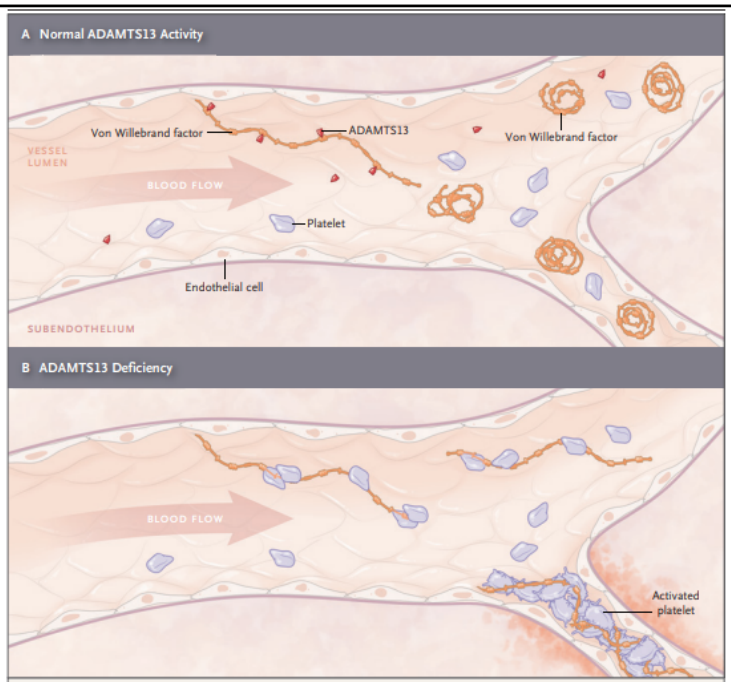
ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aPTT, activated partial thromboplastin time; INR, international normalized ratio; PCR, polymerase chain reaction.

Laurence J, Haller H, Mannucci PM, Nangaku M, Praga M, Rodriguez de Cordoba S. Atypical hemolytic uremic syndrome (aHUS): essential aspects of an accurate diagnosis. Clin Adv Hematol Oncol. 2016 Nov;14 Suppl 11(11):2-15. PMID: 27930620.

TMA– Thrombocytopenic Thrombotic Purpura (TTP)

- TMA related to severe deficiency in ADAMTS13 activity
- Quite rare, about 3 to 11 cases per 1 million
- Either from autoantibody against ADAMTS13 or a congenital mutation
- ADAMTS13 cleaves von Willebrand Factor multimers
- Absence of ADAMTS13 leads to TMA
- Activity tends to range from <5% to 10% in true TTP

Kremer Hovinga JA, George JN. Hereditary Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2019 Oct 24;381(17):1653-1662. doi: 10.1056/NEJMra1813013. PMID: 31644845.



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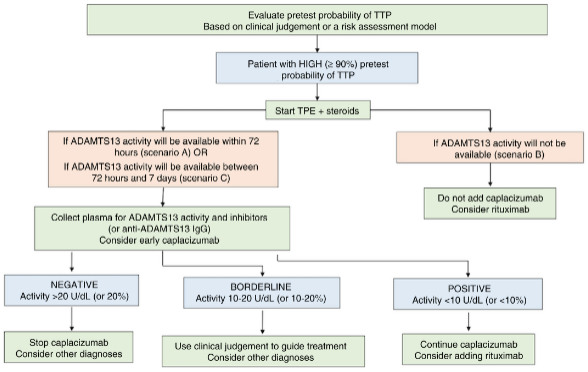
TTP Management

- Plasma exchange in the acute setting to replace deficient ADAMTS13 and remove autoantibodies
- Prophylactic replacement of plasma products in hereditary cases
- Corticosteroids, and other immune directed therapy to stop production of autoantibodies
- vWF A1 domain directed targeted therapy: Caplacizumab
- Avoid platelet transfusion



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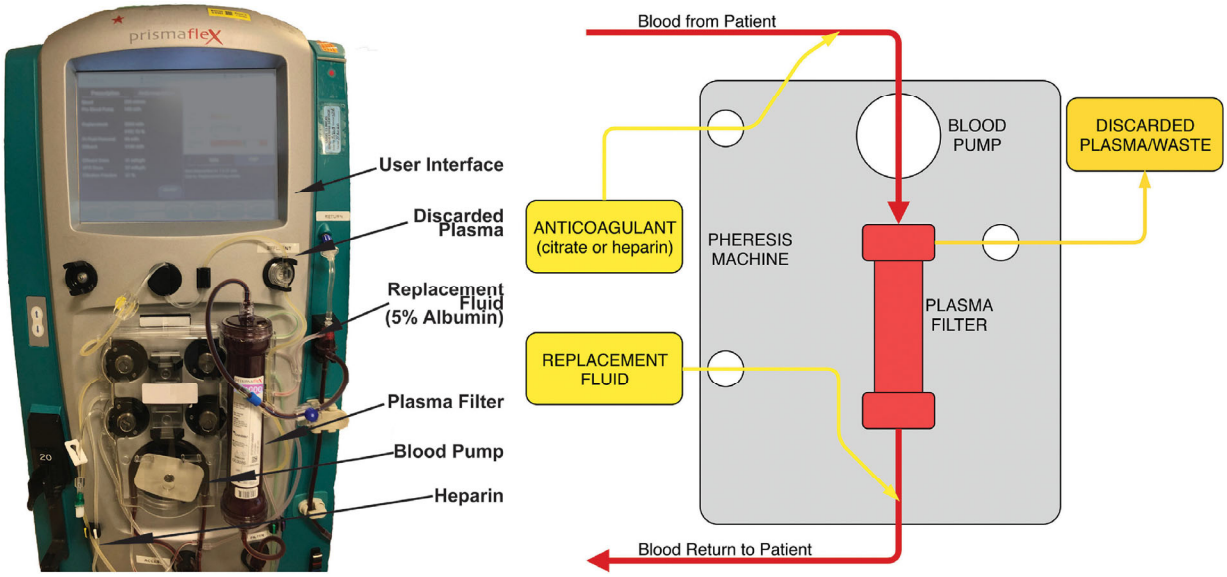
Plasma Exchange (PEX)



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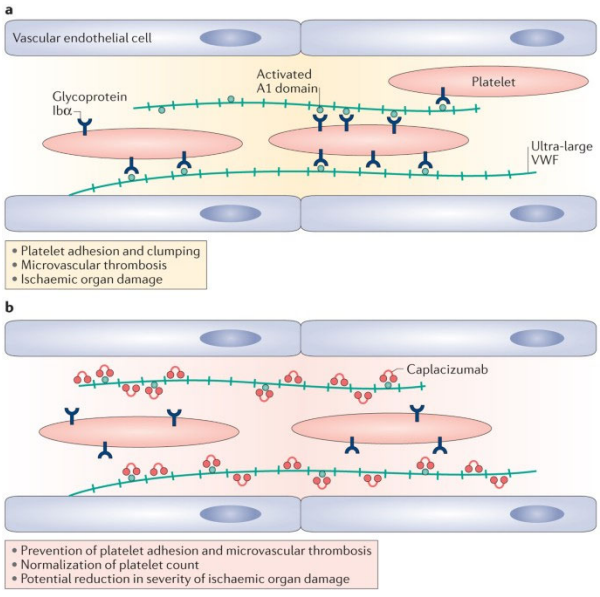
Caplacizumab



Lämmle B. Thrombotic microangiopathy: Caplacizumab accelerates resolution of acute acquired TTP. Nat Rev Nephrol. 2016 May;12(5):259-60. doi: 10.1038/nrneph.2016.47. Epub 2016 Apr 4. PMID: 27041061.

Nature Reviews | Nephrology

TMA – Hemolytic Uremic Syndrome (HUS)

- TMA caused by dysregulation of the complement cascade
- More common in children, but in adults atypical HUS can range from 0.23-1.9/million with STEC at 1-3/100,000
- Associated with either a toxin from a bacteria, a secondary condition, or a primary inherited defect
- Left untreated, carries a high morbidity and mortality

Yan K, Desai K, Gullapalli L, Druyts E, Balijepalli C. Epidemiology of Atypical Hemolytic Uremic Syndrome: A Systematic Literature Review. *Clin Epidemiol*. 2020;12:295-305. Published 2020 Mar 12. doi:10.2147/CLEP.S245642

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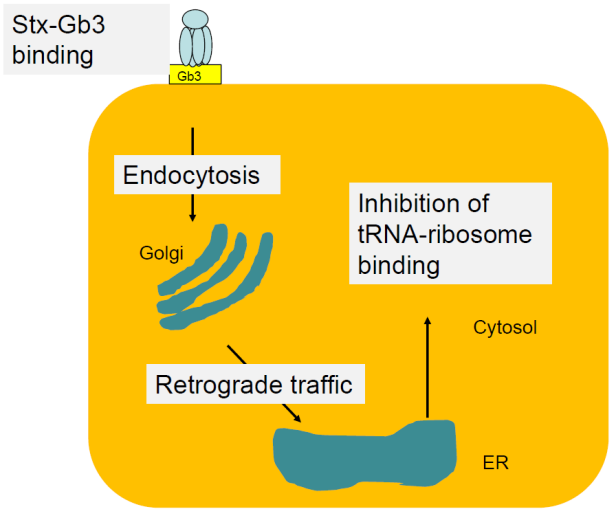
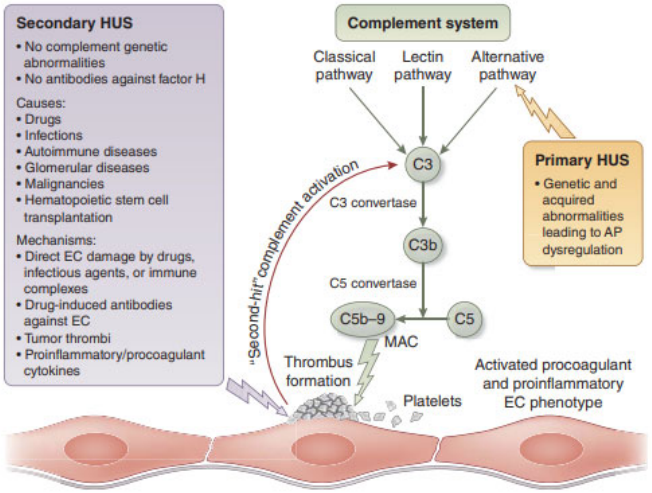
Shiga-Toxin Producing E. coli associated Hemolytic Uremic Syndrome (STEC-HUS)



Valerio E, et al. Toxins 2010;2:2359-410

HUS - Pathogenesis



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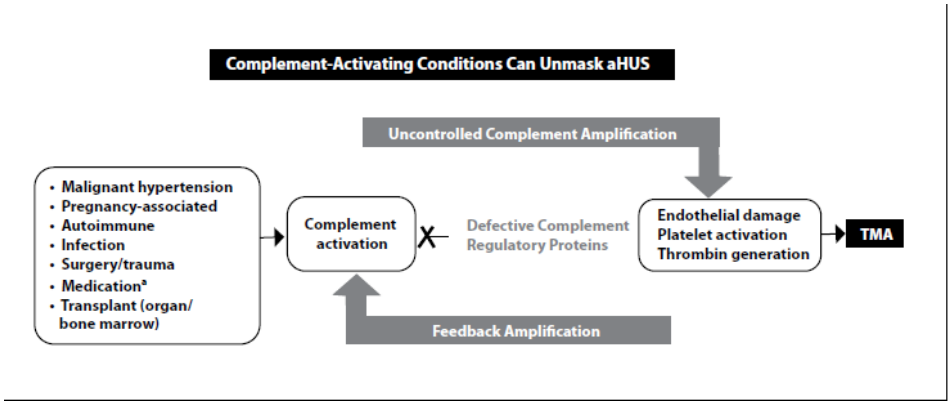

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• Malignant hypertension
• Pregnancy-associated – Preeclampsia and eclampsia – HELLP syndrome
• Autoimmune diseases – SLE – Scleroderma – APLS – Vasculitis
• Glomerulonephritis – C3GN – IgA nephropathy
• Infection
• Malignancy
• Surgery or trauma
• Drug therapy – Immunosuppressive agents – mTOR inhibitors – Chemotherapy – Antitumor agents – Antimalarial agents – Antiplatelet therapies – Antiviral agents – Oral contraceptives – Illicit drugs
• Solid organ/bone marrow transplant

APLS, antiphospholipid syndrome; C3GN, C3 glomerulonephritis; HELLP, hemolysis, elevated liver enzymes, low platelet count; IgA, immunoglobulin A; mTOR, mammalian target of rapamycin; SLE, systemic lupus erythematosus.

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HUS - Management

- Usually supportive care for STEC-HUS
- Directed treatment toward cause of secondary TMA
- Immunosuppressive therapy for autoantibodies (such as CFH)
- Plasma exchange in the acute setting when diagnosis is not clear
- Targeted therapy to elements of the complement pathway: Eculizumab, Ravulizumab

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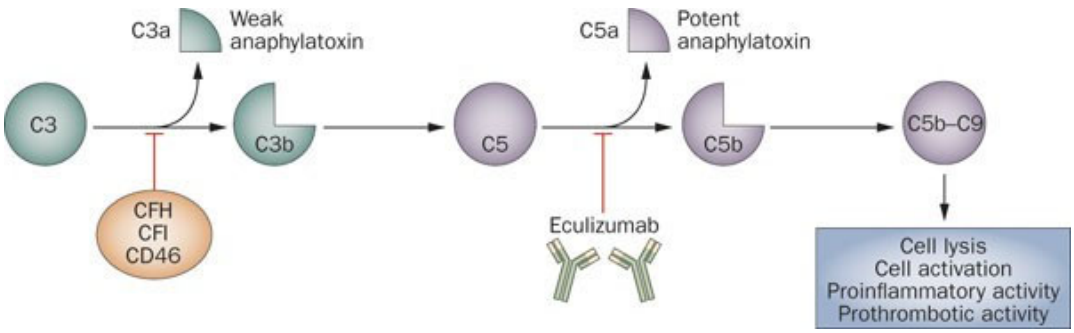
Fremeaux-Bacchi V, et al. Clin J Am Soc Nephrol 2013;8:54-62

Eculizumab / Ravulizumab



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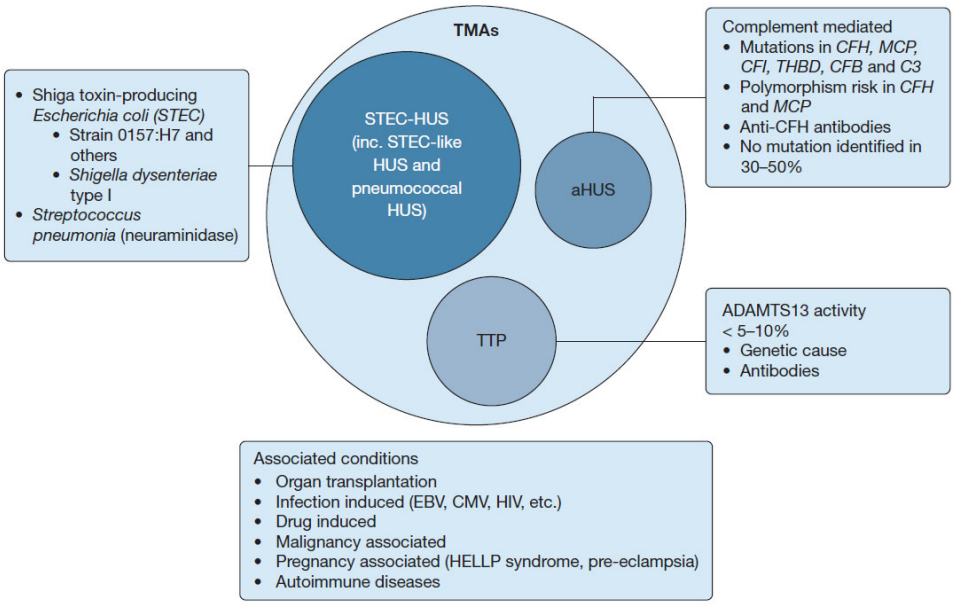

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TMA - Diagnosis

- Almost more important to the management of a TMA is recognition of a TMA
- Recognition begins by seeing a diminished platelet count along with signs of hemolysis
- These are accompanied by suspicious symptoms
- Disseminated intravascular coagulation (DIC) should be kept in the differential, thus, a PT/PTT are important to obtain
- Clinical symptoms may manifest prior to certain laboratory findings

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TMA - Diagnosis

- While STEC-HUS is classically thought to be associated with bloody diarrhea, up to 30% of aHUS and TTP cases may involve diarrhea, making stool testing paramount
- While renal involvement is more predominant in aHUS, up to 50% of TTP cases may have some renal involvement as well, though less severe than in aHUS
- TTP platelet counts tend to have median of <20,000 with aHUS platelet counts typically having median between 30,000 to 40,000
- Serum Cr values for aHUS tend to range from 1.7mg/dL to 2.3mg/dL or above

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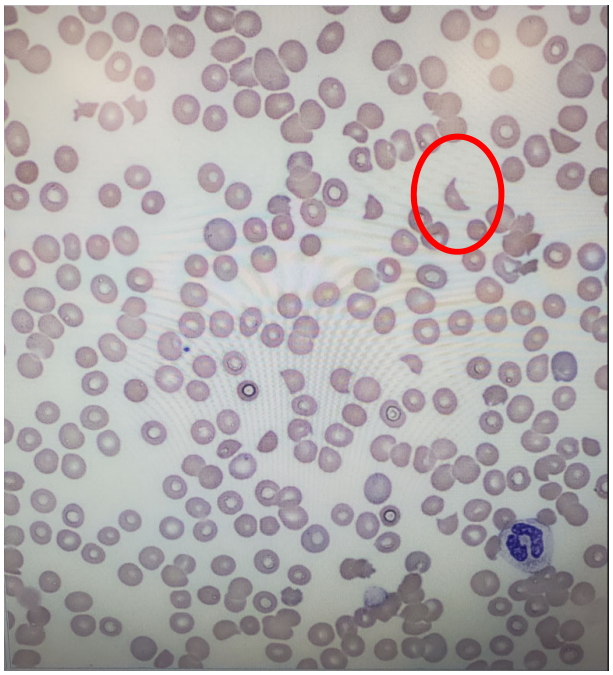

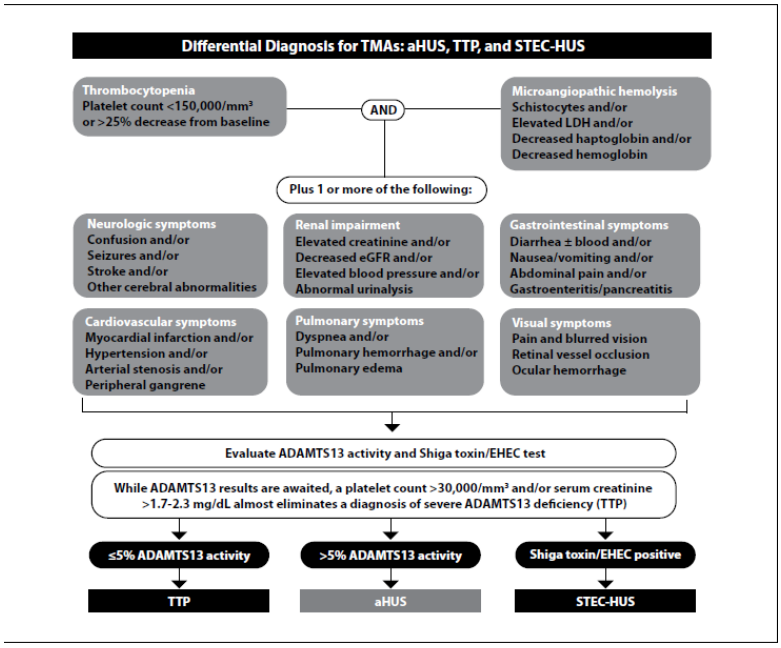

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TMA – When to Consult Hematology

- Upon suspicion of TMA
- If platelet count is dropping without an obvious cause
- If there is concern for developing hemolysis
- Abnormal/dropping platelet count paired with concerning symptoms
- *Upon suspicion of TMA*

TMA – Vignettes and Questions

A 45-year-old woman is evaluated in the emergency department for a 1-day history of abdominal pain and fever. She also reports unexpected, heavy menstrual bleeding of 1 day's duration and easy bruising of 2 days' duration. Medical and family histories are unremarkable, and she takes no medications.

On physical examination, the patient is oriented to person and place, but not time. Temperature is 38.1C (100.6F), blood pressure is 170/98mmHg, pulse rate is 110/min, and respiration rate is 20/min. Other than Confusion, neurologic examination is normal. Subconjunctival hemorrhages are present. Cardiopulmonary examination is normal. Abdominal examination reveals tenderness to palpation without guarding or rebound. Pelvic examination shows blood in the vaginal vault with no cervical motion tenderness or adnexal masses.

Laboratory studies:
Hematocrit 26%, Leukocyte count 10,300/uL, Platelet count 24,000/uL, Reticulocyte count 8.3% of erythrocytes, Bilirubin, total 2.3mg/dL, Creatinine 3.2mg/dL, Lactate dehydrogenase 1500U/L

Which of the following is the most appropriate diagnostic test to perform next?
A. ADAMTS-13 activity level
B. Osmotic fragility test
C. Peripheral blood smear
D. Stool Shiga toxin assay

Eisenstaedt R et al. Hematology and Oncology. ACP MKSAP 17. 2015.

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A 32-year-old male was admitted to the hospital after developing nausea/vomiting and severe abdominal pain. He is diagnosed with acute pancreatitis. He is recovering from this episode of pancreatitis that is likely alcohol related.

Four days into his hospitalization, his hemoglobin drops from 12.6g/dl to 9.1g/dl and he becomes acutely thrombocytopenic. His current platelet count is 65,000. He has not been on any anticoagulation including no heparin prophylaxis. A smear is reviewed and several shistocytes are seen.

He develops mental status changes and renal failure. His current creatinine is 1.4mg/dl. ADAMTS13 is sent for but the results are pending. A DIC panel is unrevealing. What initial therapy should be started?

A. FFP
B. Cryoprecipitate
C. Heparin drip
D. Plasmapheresis
E. Exchange transfusion

Garg, Ravin MD. Platelet Disorders and Thrombocytopenias. HemeOncQuestions.com. 2021.

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A 50-year-old male with a history of high-risk AML undergoes an allogeneic transplantation from his brother as consolidation. He is initially on tacrolimus to prevent GVHD, but this medication was stopped by day 120. He was doing well until day 184 after transplantation. At that time, he developed a fever and jaundice.

Labs reveal signs of hemolysis: indirect bilirubin=7.6mg/dL, LDH=546IU/L, and a haptoglobin that was undetectable. His platelet count dropped from 85,000 to 18,000 and his hemoglobin has dropped from 10.2g/dL to 7.1g/dL.

His AST, ALT, PT, PTT, Fibrinogen, and Creatinine are all normal. He has no skin lesions or diarrhea. He denies having any abdominal pain. Coombs test is negative and a blood smear reveals 4 schistocytes/HPF. The ADAMTS13 is 85%. What is the most likely diagnosis.

A. TTP
B. Vasocclusive disease of the liver
C. Tacrolimus-induced thrombotic microangiopathy
D. Transplant-associated thrombotic microangiopathy
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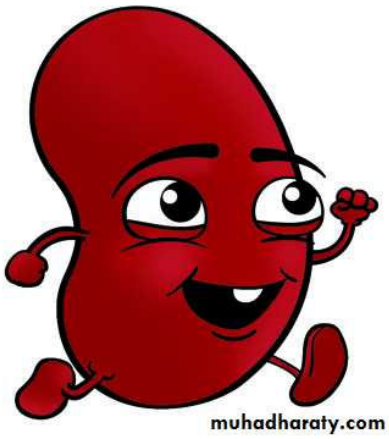
Summary

- TMA's represent a dangerous group of conditions involving complement or vWF dysfunction leading to dropping platelet counts and microthrombi causing hemolysis
- Untreated, they have a high morbidity and mortality
- Recognition of their development is vitally important, as is Hematology consultation

Questions?



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