Thrombocytopenia:
The common, coincidental, and the complicated

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Disclosures

• Sanofi Genzyme:	Research funding and consulting fees
• Alexion:	Research funding and consulting fees
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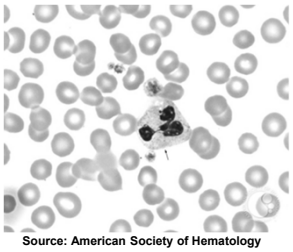
DPSKAMATTD

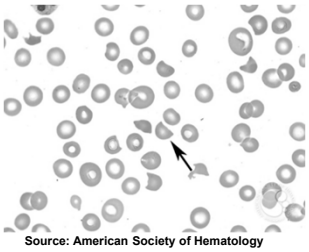
- Venous Thromboembolism
- Hemochromatosis
- Heparin-Induced Thrombocytopenia
- Thrombotic Thrombocytopenic Purpura
  - atypical Hemolytic Uremic Syndrome (aHUS)

Lawrence Rice, The Methodist Hospital, Weill Cornell Medical College, Houston, TX

Thrombocytopenia

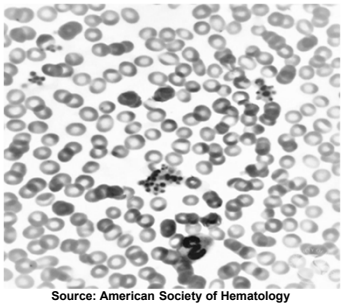


Source: American Society of Hematology



Source: American Society of Hematology

Spurious Thrombocytopenia



Source: American Society of Hematology

Definition of Thrombocytopenia

- Thrombocytopenia: abnormally low number of platelets in the peripheral blood
  - Confirmed by peripheral smear review
- Differing degrees of thrombocytopenia:
  - "Normal" typically 150-400 x 10^9/L
  - >50 x 10^9/L acceptable for surgery for most patients
  - >30 x 10^9/L safe level/goal for treating ITP
  - <10 x 10^9/L increased risk for spontaneous bleeding

Approach to Thrombocytopenia

- Conditions that need to be considered:

Acute/Unique Therapy Required
- Heparin Induced Thrombocytopenia
- Thrombotic Thrombocytopenic Purpura
- Atypical Hemolytic Uremic Syndrome
- Immune Thrombocytopenic Purpura

- Thrombocytopenia Causes
  - "Hospital acquired thrombocytopenia"
    - Drug induced
    - Acute illness related
      - Consumption/production issues

Thrombocytopenia and Sepsis/Infection

- Mild/transient thrombocytopenia common in systemic infection
  - Decreased production
  - Increased destruction
  - Increased splenic sequestration
- Viral infections can impair platelet production, increased destruction
  - HIV, CMV, Hepatitis C
  - Same infections also associated with immune mediated thrombocytopenia

Thrombocytopenia in Critical Illness

- Critically ill patients frequently develop thrombocytopenia
  - Typically mild to moderate
  - 5% will develop platelet counts < 50K
    - May be associated with bleeding
- Mechanism of thrombocytopenia
  - Enhanced clearance
  - Impaired production
- Diagnosis
  - Prior platelet counts to hospitalization very helpful

Thrombocytopenia in Intensive Care

Prospective observational cohort study

-329 patients consecutively admitted to medical-surgical ICU

-136/329 (41%) at least one platelet count <150K

-higher organ dysfunction scores, longer ICU stays, higher mortality (5.0, CI 2.7-9.1)

Vanderschueren et al Crit Care Med 2000v28, p 1871-76

Thrombocytopenia in Intensive Care

Table 2. Causes of thrombocytopenia

	No. (%)
Sepsis (all)	65 (47.8)
Sepsis with documented bacteremia	38 (27.9)
Other infection	15 (11.0)
Overt DIC	19 (14.0)
Primary hematologic disorder	12 (8.8)
Liver disease/hypersplenism	25 (18.4)
Alcoholism	7 (5.1)
Massive transfusion	10 (7.4)
Cytostatic drugs	9 (6.6)
Other medications	12 (8.8)
Other causes	9 (6.6)
Unknown cause	19 (14.0)
More than one cause	35 (25.7)

DIC, diffuse intravascular coagulation.

In 35 patients, more than one cause was present, so the cumulative percentage adds up to >100%.

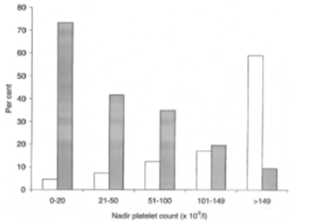


Figure 2. Distribution of patients according to nadir platelet count (*white bars*) and relative mortality per nadir platelet count category (*gray bars*).

Vanderschueren et al Crit Care Med 2000v28, p 1871-76

Drug Associated Thrombocytopenia

- Many drugs reported to cause thrombocytopenia
  - Decision on which drugs to discontinue can be difficult
- Most common agents:
  - Quinine, quinidine, phenytoin, gold, prednisone, rifampin, valproate
  - Evidence for causality typically weak
  - Diagnosis supported by recovery platelet count in 5-7 days

Drug-Induced Thrombocytopenia

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- Timing ontext of clinica
  - Oth
  - Pri
  - Pot

Drugs associated with isolated thrombocytopenia

Drug	Mechanism(s)
Abciximab	DITP
Acetaminophen	DITP with antibodies to a drug metabolite; the antibodies do not react with the unmodified parent compound
Alemtuzumab	ITP-like syndrome*
Amiodarone	DITP
Beta-lactam antibiotics (eg, penicillins, cephalosporins)	DITP
Carbamazepine	DITP
Eptifibatide	DITP
Ethambutol	DITP
Furosemide	DITP
Gold compounds	Bone marrow suppression
Haloperidol	DITP
Heparin	Drug-dependent antibodies that also activate platelets and cause endothelial injury
Ibuprofen	DITP in some patients; in other patients only antibodies to a drug metabolite that do not react with the unmodified parent compound
Irinotecan	DITP
Levofloxacin	DITP
Linezolid	Bone marrow suppression (dose-dependent)
Measles-mumps-rubella (MMR) vaccine	ITP-like syndrome
Naproxen	DITP with a antibodies to a drug metabolite; the antibodies do not react with the unmodified parent compound
Oxaliplatin	DITP
Phenytoin	DITP
Piperacillin	DITP
Quinidine	DITP
Quinine†	DITP
Ranitidine	DITP
Rifampin	DITP
Simvastatin	DITP
Sulfonamides	DITP
Tirofiban	DITP
Trimethoprim-sulfamethoxazole	DITP
Valproic acid	Bone marrow suppression (dose-dependent)
Vancomycin	DITP

Thrombocytopenia and Liver Disease

- Splenic sequestration
  - All normal splenic functions accentuated in the enlarged spleen
  - Typically affects the platelets and the WBC
  - Lower measured platelet count in blood but…..
    - Bleeding rare
    - Normal platelet mass

Thrombocytopenia Secondary to Sequestration

- Normally 1/3 of platelets sequestered in spleen
- Extensive splenomegaly
  - Up to 90% of platelets may be sequestered
- Associated Conditions
  - Portal hypertension/Cirrhosis
  - Splenomegaly
- "Apparent Thrombocytopenia"
  - Rarely clinical bleeding because platelet mass normal
    - Hepatic failure patients

Liver Disease/Splenomegaly and Thrombocytopenia

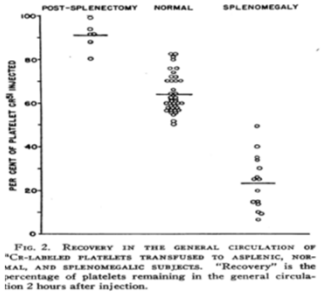
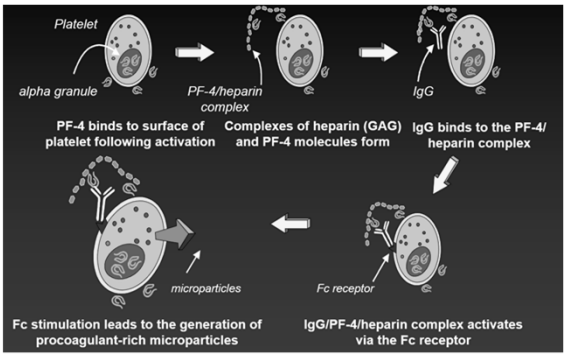


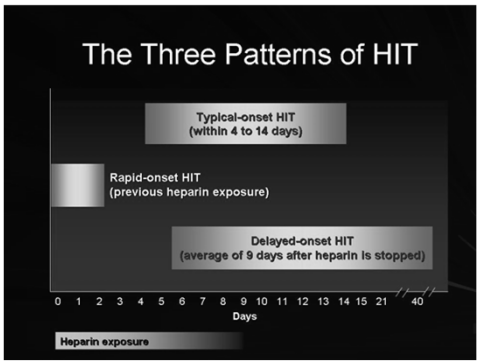
FIG. 2. RECOVERY IN THE GENERAL CIRCULATION OF ^{51}Cr-LABELED PLATELETS TRANSFUSED TO ASPLENIC, NORMAL, AND SPLENOMEGALIC SUBJECTS. "Recovery" is the percentage of platelets remaining in the general circulation 2 hours after injection.

Aster, R. Journal of Clinical Investigation 1966. v45, p.645-57.

Pathophysiology of Heparin Induced Thrombocytopenia



Courtesy of Dr John G. Kelton, McMaster University



Frequency of HIT Related Complications

- Deep venous thrombosis 50%
- Pulmonary embolism 25%
- Acute systemic reaction 25%
- Skin lesions at injection site 10%–20%
- Acute limb ischemia 5%–10%
- Warfarin-associated venous limb gangrene 5%–10%
- Acute thrombotic stroke or MI 3%–5%

Warkentin TE. *Thromb Haemost.* 1999;82:439-447.

Heparin Induced Thrombocytopenia-Treatment

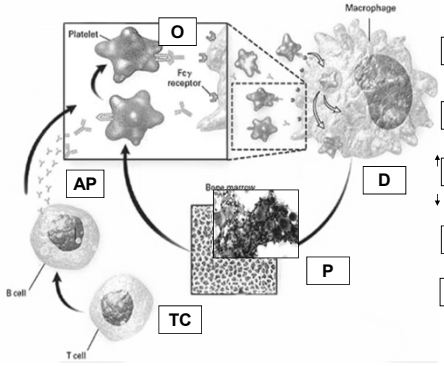
- **Discontinue heparin administration**
  - including unintended heparin exposures, catheter flushes, arterial line flushes, etc.
  - LMWH
- **Systemic anticoagulation with a direct thrombin inhibitor (DTI)**
  - Cannot wait for results of serologic testing
  - Argatroban and Lepirudin approved for treatment by the United States FDA (Pradaxa/Dabigatran)

Immune Thrombocytopenic Purpura (ITP)

- Isolated thrombocytopenia (< 100 x 10^9/L) with otherwise normal CBC and peripheral smear
  - No findings on CBC suggestive of alternative diagnosis
- Mucocutaneous bleeding
- No other conditions that can cause thrombocytopenia, liver disease, HIV, HCV, myelodysplasia, drugs, etc

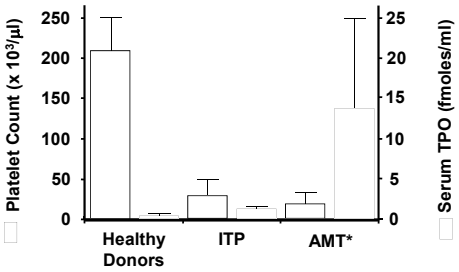
George JN, et al. *Blood*. 1996;88:3-40

Pathophysiology of ITP



Cines DB, Blanchette VS. *N Engl J Med*. 2002;346:995-1008.

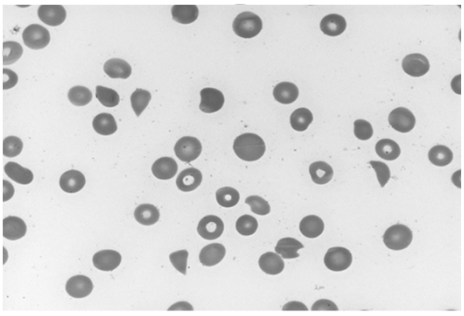
Thrombopoietin Levels in ITP



Mukai HY, et al. *Thromb Haemost.* 1996;76:675-678.

*Amegakaryocytic thrombocytopenia

Thrombocytopenia and Thrombotic Microangiopathy



Thrombocytopenia and the Kidney

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Disclosures

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Representative Case Study

- **23 year old previously healthy Caucasian female is 2 weeks post-partum and admitted with altered sensorium. Over the past week she complained of fatigue, headache, shortness of breath, and decreased urine output. Blood pressure was 190/110 mm Hg on presentation. Head CT was negative.**
- **This was the patient's first pregnancy and it was uneventful.**

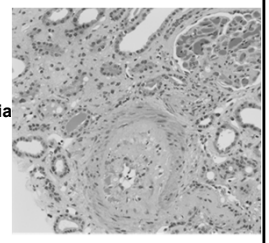
Initial Laboratory Evaluation

- **Hematology:**
  - **WBC: 15.5**
  - **Hgb: 7.5**
  - **Platelets: 46,000**
  - **PTT – 28 INR – 1.0**
  - **Fibrinogen – 300**
  - **D-dimer – 11.5**
  - **LDH: 1900**
  - **Haptoglobin < 6**
- **Chemistries:**
  - **Na: 142**
  - **K – 5.0**
  - **BUN: 95**
  - **Serum CR: 5.3 mg/dl**
  - **AST, ALT – Normal**
  - **Albumin – 2.5**

- **Peripheral Smear: 3+ Schistocytes**
- **Urinalysis: moderate blood, >300 mg/dl protein,**
- **Urine Microscopy: 5-10 acanthocytes/hpf, + granular casts**

Defining Thrombotic Microangiopathy (TMA)

- TMA is caused by abnormalities in the vessel wall of the arterioles and capillaries causing microvascular thrombi
- The key features of TMA are:
  - Thrombocytopenia – Consumptive
  - Microangiopathic Hemolytic Anemia (MAHA)
  - ± target organ damage (CNS, Renal, Cardiac)
- Why should we care?
  - Life-threatening disorders – early diagnosis and treatment is essential
  - Management of TMA depends on its cause



Primary and Secondary causes of TMA

Primary TMA Syndromes	Secondary TMA Syndromes
1. Thrombotic Thrombocytopenic Purpura (TTP)	1. Shiga toxin producing E. Coli Hemolytic Uremic Syndrome (STEC-HUS)
2. Atypical hemolytic uremic Syndrome (aHUS)	2. Autoimmune disease (SLE, scleroderma)
3. Anti-phospholipid syndrome	3. Malignant Hypertension
4. Coagulation-mediated TMA	4. Pre-eclampsia/HELLP
5. Cobalamin C deficiency (rare, newborns)	5. Systemic Infection (Pneumococcal, HIV)
	6. Malignancy
	7. Hematopoietic Stem Cell Transplant
	8. Drug induced TMA

Diagnostic Approach to TMA

1. Thrombocytopenia
2. Anemia
3. ±Acute Target organ damage (kidney, heart, brain, liver, skin)

↓

Thrombocytopenia with elevated D-dimer

AND

Anemia with evidence of hemolysis?
1. Peripheral Smear with Schistocytes
2. Elevated LDH, Reticulocytosis
3. Low Haptoglobin

→ NO → Thrombocytopenia and anemia are from another cause (eg. Bone Marrow Suppression, Idiopathic Thrombocytopenic purpura (ITP))

↓ YES

Consumptive Thrombocytopenia and Microangiopathic Hemolytic Anemia (MAHA) = Clinical Hallmarks of TMA

Diagnosis of TMA – Step 1

Diagnosis Step 1 → Patient with evidence of:
1. Thrombocytopenia
2. MAHA
3. ± Acute Organ damage

↓

Secondary TMA? → YES → Treat underlying cause

↓ NO

Patient has Primary TMA
1. TTP – Acquired (95%) or Congenital (<5% of cases)
2. Complement Mediated TMA (aHUS)
3. Anti-phospholipid Syndrome

Diagnosis Step 2 – Diagnosis of Primary TMA

TTP	APLAS Nephropathy	Atypical HUS
• ADAMTS13 activity < 10% (<5% also reported) • 95% of cases are acquired • Most cases have an IgG antibody to ADAMTS13 • Untreated = 90% mortality	• Thrombosis at any level of the renal vasculature • Positive serum testing for: - Lupus Anticoagulant And/Or - Anti-Cardiolipin Abs (esp. IgM or IgG) And/Or - Elevated Beta-2 Glycoprotein • Diagnosis: 1 clinical manifestation and 1 lab finding	• Clinical diagnosis • Evaluate for Alternative complement pathway activation • Low Serum C3 in 50% of cases • Complement Mutation studies should be obtained but takes time and does not play a role in the initial management

Treatment of TMA – Acute Management

Suspected TMA – thrombocytopenia and MAHA with evidence of organ failure

↓

Identifiable Cause? → **Yes** → **Treat underlying cause. Hold offending agent if drug toxicity suspected.**

↓ **No**

Labs to obtain before treatment:
1. Hemolysis Labs
2. ADAMTS13 levels
3. Anti-phospholipid Abs
4. Serum Complement Levels
5. Autoimmune serologies

↓

Initiate Urgent PLEX with FFP
Start empiric IV Glucocorticoids
Continue diagnostic evaluation

In the patient presenting with malignant HTN and TMA…

author: Phichet9707 (CC BY-SA 3.0)

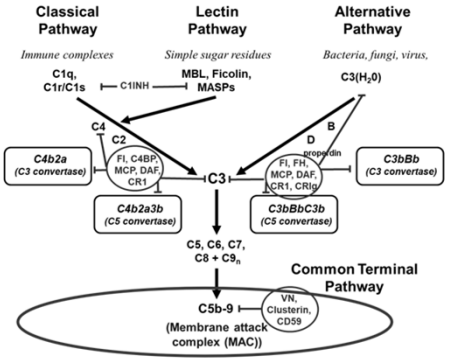
- Malignant HTN is a common presenting feature of TMA
- Malignant HTN is the cause of TMA – BP control alone causes progressive improvement in all TMA manifestations usually within a few days
- Primary TMA is the cause of TMA - Patient with new onset HTN or previously well controlled HTN presenting with malignant HTN and TMA.

- Work up for chronic changes related to hypertension (ie. Fundus exam to assess for retinopathy or echo to assess for LVH)

Atypical Hemolytic Uremic Syndrome

- aHUS is a life-threatening disorder due to congenital or acquired dysregulation of the alternative complement pathway
  - Unchecked alt. complement activation, endothelial damage and thrombosis.
- 10-15% mortality rate with each flare; 50% risk of ESRD
- In 1998 complement factor H was found to be associated with atypical HUS
- Over 100 different mutations have been identified in CFH gene alone. Additional mutations identified in CFI, and CD46 (MCP)
  - Gain of function mutations identified in CFB and C3.
  - Anti-CFH antibodies found in sporadic forms

Pathophysiology of aHUS: Alternative Complement Activation



Slide Courtesy of Dan Birmingham, PhD

aHUS: A Diagnostic Challenge

- **Severe neurologic manifestations may occur similar to TTP**
- **Diarrhea in 30% of cases so cannot easily differentiate from STEC-HUS**

	ADAMTS13 Severe Deficiency		ADAMTS13 Non-Deficient	
	Platelets ($x10^9$/L)	Serum Creatinine (mg/dl)	Platelets ($x10^9$/L)	Serum Creatinine (mg/dl)
Raife et al	13	1.2	44	2.7
Coppo et al	17	1.3	67	5.1
Kremer et al	11	1.6	22	4.6
Cataland et al	12	1.7	66	6.7
Bentley et al	16	1.1	64	3.5
Averages	**14**	**1.4**	**53**	**4.5**

Cataland et al Blood 2014

Treatment of Atypical HUS

PLEX in atypical HUS

- **Retrospective study of 273 patients with aHUS to determine role of complement in predicting clinical phenotype and response to treatment**
  - **Overall 55% of adults and 80% of children responded to PLEX therapy**
  - **Excluding MCP, complete remission rate was only 5-43%**
  - **Hematologic response did not correlate with renal response. 48% of children and 67% of adults reached ESRD despite hematologic response with PLEX**

Complement Mutation	ESRD or Death at 3 years	Response to PLEX	Kidney Txp survival at 1yr
CFH	49 (77%)	57 (63%)	5 (29%)
MCP	1 (6%)	28 (96%)	3 (100%)
CFI	6 (60%)	2 (25%)	2 (33%)
C3	8 (67%)	8 (57%)	4 (57%)

- **Overall PLEX is effectively controls aHUS in 30-40% of cases**

Norris et al. CJASN 2010

Eculizumab for treatment of aHUS

- Eculizumab – monoclonal antibody to complement C5 blocking its cleavage and preventing production of the terminal complement components C5a and the membrane attack complex C5b-C9.
- Inhibition of terminal complement activation reduces endothelial damage and thrombosis.
- In 2011, Eculizumab was FDA approved for treatment of atypical HUS.

Standard Dosing: 900mg IV weekly X 4 weeks followed by 1200mg IV every 2 weeks for maintenance

Trial 1: PLEX Refractory patients (≥ 4 sessions)

1. 4/5 patients who required dialysis at baseline were liberated and remained dialysis free at 64 weeks
2. Mean increase in eGFR of 32ml/min/1.73m^2 at 26 weeks (P=0.001) and maintained at 64 weeks
3. Earlier intervention with Eculizumab associated with a greater improvement in eGFR (P=0.007)
4. Platelet counts normalized in 88% of patients by week 64
5. 88% of patients were TMA free at week 64

Legendre et al NEJM 2013

Trial 2: PLEX Dependent patients (≥ 8 weeks)

1. PLEX was discontinued in all patients and did not have to be resumed
2. Mean increase in eGFR was 6 ml/min/1.73m^2 at week 26 (P<0.001) and 9 ml/min/1.73m^2 at 62 weeks (P=0.003)
3. Two patients who required dialysis at baseline did not improve
4. Earlier intervention with Eculizumab was associated with significantly greater improvement in eGFR (P<0.001).
5. 90% had normalization of platelets at 26 weeks
6. 85% were TMA free at week 62

Legendre et al NEJM 2013

How long do we treat?

- Is it okay to stop treatment for patients who attain remission?
- Overall 48 reports of patients taken off therapy with 26% relapse risk
- Study of 10 patients with aHUS where Eculizumab was stopped
- In total 7/10 patients remained relapse free after stopping Eculizumab for a median follow up of 12.7 months.
- Higher relapse risk associated with CFH mutation and high titer FHAA

Ardissino et al. AJKD 2014

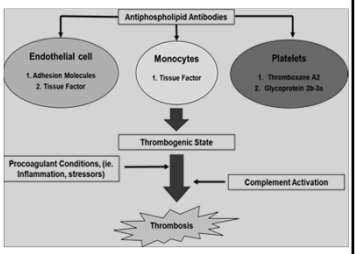
Eculizumab – Adverse Effects

- Increased risk for infection from encapsulated organisms
- Eculizumab treated patients 1000-2000x greater risk than general pop.
- **All patients should receive meningococcal vaccine prior to treatment**
- Protocol: Vaccinate for *N. Meningitis* and treat with prophylactic antibiotics for the first 2 weeks post vaccine.
- *N. Meningitis type B* is not covered by the quadrivalent vaccine and the recent sergroup B vaccines is also recommended.
- Vaccine is not completely protective and prophylactic antibiotics while on therapy and up to 3 months after stopping treatment has been recommended.
- Between 2008-2016 there have been 16 reported cases in the US of meningococcal disease associated with Eculizumab.
  - 14 cases occurred after at least 1 dose of vaccine

McNamara et al. CDC 2017
Goodship KDIGO KI 2017

The Anti-phospholipid Syndrome

- APLAS is an autoimmune disease characterized by both arterial and venous thrombosis, recurrent pregnancy loss, and persistently elevated ACL and/or Lupus anticoagulant.
- Odds of developing thrombosis (study of 7000 patients with APS)



APL Ab Status	OR for Thrombosis
LA + β2-gp	43.1
LA alone	11.5
ACL alone	1.6

Ruiz-Irastorza et al. Lancet 2010

APLAS Nephropathy

- **APLAS nephropathy - The presence of aPL Abs along with histologic detection of thrombotic microangiopathy**
- **Renal manifestations include arterial or venous thrombosis, renal infarct, malignant hypertension, nephritis, and TMA**
- **Primary or secondary disease and the kidney is a major target organ for injury.**
- **Commonly associated with SLE but can occur in the absence of other autoimmune disease**
- **Can occur with acute onset or cause insidious loss of kidney function**

Clinical Manifestations of APLAS Nephropathy	
Frequency	**Manifestations**
Common (>20%)	Venous thromboembolism Miscarriage Thrombocytopenia Recurrent Stroke Recurrent Migraine Livedo Reticularis
Less Common (10-20%)	**Valvular Heart Disease** Pre-eclampsia Coronary Artery Disease Hemolytic Anemia
Uncommon (<10%)	**Vascular Dementia** **APLAS Nephropathy** Retinal Artery Thrombosis Epilepsy Budd Chiari Syndrome Transverse Myelitis

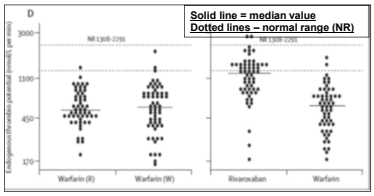
Ruiz-Irastorza et al Lancet 2010; Nochy et al. JASN 2010

Approach to Management

- **Unfractionated heparin or LMWH is used for acute thrombosis**
- **Warfarin is the standard of care for chronic management of APS with goal INR 2-3**
- **Risk of recurrent thrombosis is high - up to 30% in patients with persistently positive aPL antibodies**
  - **In most cases lifelong anti-coagulation is required**
- **Anticoagulation alone has been shown to be effective in treating APLAS and APSN.**
- **Direct Thrombin inhibitors or Factor Xa inhibitors are more commonly being used – what is the evidence?**

Direct Oral Anticoagulants in APLAS

- **RAPS study –** RCT of Warfarin vs Rivaroxaban for treatment of **low risk** APLAS – Non-inferiority trial (n=110)



- **TRAPS study - Rivaroxaban vs Warfarin in high risk patients with APLAS**
  - **Open label, multicenter non-inferiority study of 120 patients**
  - **Trial terminated early due to greater number of thrombotic events in Rivaroxaban group (11 vs 2, p=0.008) after 569 d follow up**

Cohen et al Lancet 2016, Pengo et al Blood 2018

Back to the Case

- **Patient received 4 treatments of PLEX but hemolysis and thrombocytopenia persisted**
- **Renal function continued to worsen and the patient was started on dialysis**
- **Renal biopsy confirmed presence of TMA**
- **Laboratory testing for cause of TMA:**
  - **ADAMTS13 - Normal**
  - **Stool Culture Negative for Shiga toxin**
  - **Antiphospholipid antibody - Negative.**
  - **Serum C3 – 65 (Low), C4 normal.**
- **Diagnosis: aHUS; Eculizumab was initiated**
- **Hemolysis and thrombocytopenia improved 2 days after the first dose and PLEX was stopped**
- **Renal function normalized 3 weeks after starting treatment.**
- **CFH mutation identified**
- **Remission maintained for 2 years on therapy but patient decided to stop therapy**
- **Relapsed 2 weeks after stopping treatment with anuric renal failure requiring dialysis and MAHA**
- **Eculizumab was resumed with rapid improvement and normalization of kidney function. She has remained in remission on treatment**

Conclusions

- **TMA needs to be considered for patients with thrombocytopenia and acute kidney injury.**
- **TMA syndromes are rare, life threatening diseases in which treatment differs based on cause**
- **PLEX should be started in patients who present with clinical signs concerning for TMA and a secondary cause is not immediately known.**
- **Terminal Complement blockade with Eculizumab has improved outcomes in aHUS and is the preferred treatment of choice in patients where aHUS is suspected.**
- **APLAS nephropathy is an under recognized cause of TMA. Treatment with anti-coagulation with warfarin is recommended. Immunotherapy is reserved for resistant cases**