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
- Regeneron: Consulting fees
DPSKAMATTDD

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

Thrombocytopenia

Source: American Society of Hematology
Spurious Thrombocytopenia

源：美国血液学会

- 血小板减少症：外周血中血小板异常低的数目
  - 确认通过外周血涂片审查

- 不同程度的血小板减少症：
  - “正常”典型 150-400 x 10⁹/L
  - >50 x 10⁹/L 适用于大多数患者进行手术
  - >30 x 10⁹/L 治疗ITP 安全水平/目标
  - <10 x 10⁹/L 增加自发性出血的风险

定义血小板减少症

- 血小板减少症：外周血中血小板异常低的数目
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Approach to Thrombocytopenia

- Conditions that need to be considered:
  - 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

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

- Diagnosis as an imperfect science
- Timing of thrombocytopenia in the context of clinical picture
  - Other explanations
  - Prior platelet counts
  - Potential offending agents?

- 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>MDS</th>
<th>MFD</th>
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<tr>
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<td>Tranexamic acid</td>
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<td>Warfarin</td>
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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

Pathophysiology of Heparin Induced Thrombocytopenia

- PF-4 binds to surface of platelet following activation
- Complexes of heparin (GAG) and PF-4 molecules form
- IgG binds to the PF-4/heparin complex

Fc stimulation leads to the generation of procoagulant-rich microparticles
IgG/PF-4/heparin complex activates via the Fc receptor

The Three Patterns of HIT

- Typical-onset HIT (within 4 to 14 days)
- Rapid-onset HIT (previous heparin exposure)
- Delayed-onset HIT (average of 9 days after heparin is stopped)
**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%


**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 10⁹/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


Pathophysiology of ITP

Thrombopoietin Levels in ITP


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Thrombocytopenia and Thrombotic Microangiopathy
Thrombocytopenia and the Kidney

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Disclosures

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<tr>
<th>Advisory Board</th>
<th>Alexion Pharmaceuticals, Aurinia Pharmaceutical, Aztrazeneca, Bristol Myers Squib</th>
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<tr>
<td>Grant Funding</td>
<td>Malinckrodt Fellowship Grant, Aurinia Pharmaceuticals, EMD-Serono</td>
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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**
1. Thrombotic Thrombocytopenic Purpura (TTP)
2. Atypical hemolytic uremic Syndrome (aHUS)
3. Anti-phospholipid syndrome
4. Coagulation-mediated TMA
5. Cobalamin C deficiency (rare, newborns)

**Secondary TMA Syndromes**
1. Shiga toxin producing E. Coli Hemolytic Uremic Syndrome (STEC-HUS)
2. Autoimmune disease (SLE, scleroderma)
3. Malignant Hypertension
4. Pre-eclampsia/HELLP
5. Systemic Infection (Pneumococcal, HIV)
6. Malignancy
7. Hematopoietic Stem Cell Transplant
8. Drug induced TMA
Diagnosis 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

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

Diagnosis of TMA – 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**

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

**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...

- 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**

- Classical Pathway
  - Immune complexes
  - C1q, C1r/C1s

- Lectin Pathway
  - Simple sugar residues
  - MBL, Ficolin, MakPs

- Alternative Pathway
  - Bacteria, fungi, virus
  - C3(H₂O)

**aHUS: A Diagnostic Challenge**

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

<table>
<thead>
<tr>
<th></th>
<th>ADAMTS13 Severe Deficiency</th>
<th>ADAMTS13 Non-Deficient</th>
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</thead>
<tbody>
<tr>
<td>Raife et al</td>
<td>Platelets (x10⁹/L) 13</td>
<td>Serum Creatinine (mg/dl) 1.2</td>
</tr>
<tr>
<td>Coppo et al</td>
<td>Platelets (x10⁹/L) 17</td>
<td>Serum Creatinine (mg/dl) 1.3</td>
</tr>
<tr>
<td>Kremer et al</td>
<td>Platelets (x10⁹/L) 11</td>
<td>Serum Creatinine (mg/dl) 1.6</td>
</tr>
<tr>
<td>Cataland et al</td>
<td>Platelets (x10⁹/L) 12</td>
<td>Serum Creatinine (mg/dl) 1.7</td>
</tr>
<tr>
<td>Bentley et al</td>
<td>Platelets (x10⁹/L) 16</td>
<td>Serum Creatinine (mg/dl) 1.1</td>
</tr>
<tr>
<td><strong>Averages</strong></td>
<td>Platelets (x10⁹/L) 14</td>
<td>Serum Creatinine (mg/dl) 1.4</td>
</tr>
</tbody>
</table>

*(Slide Courtesy of Dan Birmingham, PhD)*
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

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

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**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/1.73m² 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/1.73m² at week 26 (P<0.001) and 9 ml/min/1.73m² 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

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
**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

**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)

<table>
<thead>
<tr>
<th>APL Ab Status</th>
<th>OR for Thrombosis</th>
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<tr>
<td>LA + β2-gp</td>
<td>43.1</td>
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<tr>
<td>LA alone</td>
<td>11.5</td>
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<tr>
<td>ACL alone</td>
<td>1.6</td>
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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

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<th>Clinical Manifestations of APLAS Nephropathy</th>
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<tr>
<td><strong>Frequency</strong></td>
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<tr>
<td>Common (&gt;20%)</td>
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<td>Uncommon (&lt;10%)</td>
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**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**

- **RAP5 study** – RCT of Warfarin vs Rivaroxaban for treatment of low risk APLAS – Non-inferiority trial (n=110)
  - 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

- **TRAP5 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

  [Graph: Solid line = median value, Dotted lines – normal range (NR)]

Cohen et al Lancet 2016, Pengo et al Blood 2018

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**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.