Thrombotic Microangiopathy in the Critical Care Setting

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Objectives

• Review the differential diagnosis of Thrombotic Microangiopathy (TMA) in the critical care setting

• To inform on the recommended diagnostic tests and key considerations to differentiate between different underlying causes of TMA

• Discuss treatment options for management of TMAs
Disclosure

• Advisory board work for Alexion (makers of Eculizumab)
• Advisory board work for Terumo BCT (makers of Apheresis Devices)
• Apheresis physician

• From Toronto......no one outside of Toronto likes Toronto
TMA as presents below is a symptom

• CBC
  • Not need anemia
  • RBC FRAGMENTS generally 1% or greater (blood film important)
  • Not need reticulocytosis initially
  • THROMBOCYTOPENIA

• LDH
  • Elevated

• Bilirubin
  • Not necessary elevated

• Haptoglobin
  • Generally severely decreased

Tissue
  • Renal (most commonly) biopsy demonstrates occlusive microangiopathic changes however some differences between pathologic findings depending on underlying cause

• Keep in mind there can be renal isolated TMA syndromes (renal biopsy would be required in that case to gain inclusion into that diagnosis)
TMA

**DIC**
- Malignant HTN
- Sepsis/Endocarditis
- ANCA GBM
- CTD Scleroderma renal crisis

**HTN**
- Blood & urine cultures, CXR, hypotension
- ECHO

**Blood & urine cultures, CXR, hypotension**
- Rash, active joints, serositis, scleroderma
- HTN
- ANA, dsDNA, C'

**Renal failure, pulmonary hemorrhage**
- 3-4 organs involved rapidly, thrombosis, PTT, APLA

**Pregnant, HTN, LFT elevated**
- Medications: Calcineurin, quinine, clopidogrel, chemotherapy
- Novel agents
- Systemic signs, bone pain, masses, calcium

**Supportive care, find underlying cause**
- Control BP
- Anti-Biotic, Support Care
- PLEX GBM or failure ANCA, immune suppression
- Immune Suppression
- Heparin IVIG Steroid
- Deliver Control BP
- Stop Meds
- Chemo radiation
- Support Stop meds

**PLEX if ADAMTS 13, or not resolve**
- PLEX
- PLEX if not resolve
- PLEX Ticlopidine quinine
- PLEX AMR kidney

*= may indicate presence of another disease process
TMA not diagnosed from previous slide

- TTP
- aHUS
- STEC HUS
CBC

**Hemoglobin**: do not need anemia

**WBC**: leukocytosis: infection/inflammatory process/malignancy
leukopenia: infection, medication, bone marrow process

**Thrombocytopenia**
- Severe thrombocytopenia suggestive of TTP
- Moderate thrombocytopenia more suggestive of aHUS
- Coppo criteria: platelets >30x10^9/L

Reticulocyte Count

Elevated **reticulocyte count** may be suggestive of hemolysis.
In early phases of illness, may not have increased reticulocyte count.
**RBC Fragments** should be quantified by percentage

aHUS tends to have lower fragment percentage than TTP

Other disorders with fragments in background that are not TMA:
- iron deficiency
- hemoglobinopathies
- hyposplenic states
- oxidative process
- B12 deficiency/megaloblastic anemia

**Creatinine**: will help distinguish between aHUS vs TTP
Coppo criteria: Cr >150umol

**LDH critical**: normal LDH would make one reconsider TMA process initially
- LDH can normalize with progressive renal dysfunction in aHUS

**LFT** can exclude HELLP, liver damage in TMA, help interpret LDH

**Hypercalcemia** may be sign of metastatic malignancy

**Lipase** as marker of pancreatitis

**Lactate** as marker of ischemic bowel and organ damage
Coagulation tests will help exclude:

Elevated aPTT, INR. Decreased Fibrinogen: DIC or HELLP (if need to differentiate from liver failure: factor 5,7,8) Elevated aPTT: Consider CAPS

B-HCG to rule out pregnancy for HELLP, or pregnancy as underlying driver of process in TTP/aHUS/vasculitis

Urinalysis for proteinuria/RBC casts to assist in presence or cause of renal dysfunction

Signs of cardiac involvement may have prognostic and monitoring significance in TMA patient
Clinical History and Physical Exam

Medication and transplant history
Symptoms of infection, malignancy, connective tissue disorder
pregnancy history: all as cause or underlying driver of other process
Thrombosis history
Family history of renal dysfunction

Hypertension, hypotension
Cachexia, adenopathy, hepatosplenomegaly
Active joints, rash, scleroderma
Signs of thrombosis

Group and screen

To be able to provide blood products for support and treatment

Direct Antiglobulin Test

Rule out autoimmune hemolysis (although should not have predominant fragments)
Rule out pneumonia, malignancy, pulmonary hemorrhage

Rule out bleed/large stroke/venous sinus thrombosis if neurologic events
Blood and urine cultures

Rule out sepsis, endocarditis as cause of TMA
Streptococcus pneumonia (pneumococcal HUS)

Stool for shiga toxin cultures and antigen

Rule out STEC as cause of TMA

Antiphospholipid antibody screen

Rule out CAPS as cause of TMA

Haptoglobin
Evidence of intravascular hemolysis

ECHO to exclude endocarditis as cause of TMA or end organ damage as result of TMA

ANCA, antiGBM
If renal dysfunction or pulmonary hemorrhage

ANA, C₃ C₄ CH₅₀, dsDNA, ANCA, GBM
Anti ACL-70, Anti centromere

Rule out vasculitis/lupus as causes of TMA or underlying driver of other TMA process
Abdominal Imaging

If renal dysfunction to look assess kidneys
To look for malignancy as cause or underlying driver of TMA process

HIV, Hep B/C, CMV
EBV

Look for cause or underlying driver of TMA process

Homocysteine and MMA levels

Look for Cobalamin Deficiency in very young patients

Abdominal Imaging

If renal dysfunction to look assess kidneys
To look for malignancy as cause or underlying driver of TMA process
Bone marrow aspirate:
Erythroid hyperplasia and
Adenocarcinoma
ADAMTS13 activity less than 10% suggestive of TTP

*Remember to draw before plasma given*

**Decision to initiate urgent PLEX is a clinical/laboratory decision and should NOT WAIT on ADAMTS13 result**

Anti-ADAMTS13 antibody positive in most cases of acquired TTP

ADAMTS 13 activity greater than 10% *with secondary causes excluded*, need to consider aHUS
In cases where renal dysfunction of unclear etiology with no significant peripheral process. Will show evidence of TMA
Complement Functional Testing
C3, CFB, CFH, CFI
AntiCFH-Ab, C5b-9
C4d, Bb, C3a, C5a

Functional tests that may be positive in cases of complement dysregulation

Complement Genetic Testing
CFH, CFI, MCP, C3, CFB, THBD
CFHR1-5, DKGE

Can be normal in 30-50% of those with complement dysregulation

ADAMTS13
Genetic Sequencing

If no antibody detected consider hereditary TTP
Thrombotic Thrombocytopenic Purpura (TTP)

• Incidence 4-11 per million in adults
• Pentad (occurs in 4% of cases):
  • Microangiopathic hemolytic anemia (fragments)
  • Consumptive thrombocytopenia
  • Neurological deficits
  • Renal insufficiency
  • Fever
    • Other sites:
      • Cardiac
      • Gastrointestinal including diarrhea/colitis
      • Adrenal
      • Hepatic
      • Lung
      • Pancreas
  • ADAMTS13 < 10%
Standard Treatment for Acquired TTP

• Initiate therapy immediately
• Concern of death from cardiac arrhythmia/ischemia, intracranial thrombosis/hemorrhage

• Start plasma infusion and corticosteroids at referral site
  • 1mg/kg equivalent of prednisone, 1g/kg pulse can be used but never shown clearly in studies to be better
  • 30ml/kg of FFP infusion while awaiting PLEX
  • (4units FFP then 1 unit FFP over 2 hours continuously until PLEX can start)
Plasma Exchange

- **Transfer for Plasma Exchange as soon as possible**
  - Start 1.5 plasma volumes (FFP/CSP/SDP)
  - Daily PLEX
    - Death @ 6 months: >90% nothing/50% plasma infusion/22% PLEX – Rock 1991
    - Clinical signs abate (ie. Neuro, cardiac etc)
    - Normalize platelets and LDH
  - Treat underlying causes
    - Start ASA 81mg and LMWH prophylaxis when plt>50
    - PLEX 1.5 plasma volume until platelets >100 for 2 days
    - PLEX 1.0 plasma volume for 10 days total or daily until platelets >150 for 2 days
    - If no significant response by 5-7 days (and stable) consider alternate therapies
    - If critically ill and no response by 2-3 days consider alternate therapies
  - make sure rule out other issues: WRONG DIAGNOSIS, sepsis, HIT
  - No platelet transfusion unless life or limb risk bleeding
Atypical Hemolytic Uremic Syndrome

- Incidence 2-3 per million in adults
- Microangiopathic hemolytic anemia (fragments)
- Consumptive thrombocytopenia (Generally between 30-60x10⁹/L)
- Renal insufficiency
  - Creatinine >150-200 umol/L
  - This is thought to differentiate between TTP
  - 10% of TTP can have acute renal failure -Hovinga J. Blood 2010
- Other organs:
  - CNS, Cardiac, Pancreas, Respiratory, GI, colitis (diarrhea with or without blood), liver, skin
- Hypertension (in some cases difficult to treat) may be associated
- ADAMTS13 >10%
* = may indicate presence of another disease process

70% of cases triggered by:
- Infection (URTI, gastroenteritis) (40% of cases)
- Transplantation
- Malignant hypertension
- Pregnancy (20% of 1st cases, most post partum)
- Cyclosporine
- Cancer/Chemotherapy
- Connective tissue disorder
- Glomerulonephropathy

- Each of these disorders is also a cause of TMA on its own. Therefore, care is required to distinguish between these alone, and these disorders triggering aHUS complement dysregulation process
  - the requirement of a trigger (and the degree of that trigger) may be related to the underlying susceptibility of that individual due to underlying complement mutation risk

Standard Treatment of aHUS

- Blood pressure control
  - Ongoing difficult to control hypertension can be a sign of aHUS

- Renal support:
  - Renal replacement therapy
  - Electrolyte management

- Treat underlying trigger (infection, inflammation, pregnancy, discontinue offending medications etc)

- No platelet transfusions unless life or limb risk bleeding

- Plasma therapy:
  - No prospective trials in plasma therapy in aHUS
  - FFP:
    - Replenish: CFH, CFI, CFB, C3
  - PLEX:
    - Removes mutant CFH, CFI, CFB, C3
    - Removes anti-CFH antibodies and other circulating triggers of endothelial dysfunction and platelet hyperaggregability
    - Prevents volume overload from large volumes of plasma
aHUS therapy

• Start PLEX:
  • 1.5 plasma volumes
  • Replace with FFP
  • Daily until:
    • Normalize platelets and LDH
    • Hemolysis resolves
    • *Renal function stable or improving*
      • Stabilization or improvement in other end organs
  • If controlled:
    • Start taper of PLEX
  • If not controlled by 4-7 days this suggests that your initial plasma therapy will not be enough to control this process
  • *Even if platelets and LDH improving, but renal function deteriorating, this is a sign that disease process is NOT controlled*
• At this point, medical therapy should be used instead of plasma therapy
• Complement blockade should be considered as next line of therapy
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein Affected</th>
<th>Main Effect</th>
<th>Frequency</th>
<th>Response to Short-Term Plasma Therapy</th>
<th>Long-Term Outcome</th>
<th>Outcome of Kidney Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>Factor H</td>
<td>No binding to endothelium</td>
<td>20–30</td>
<td>Rate of remission: 60% (dose and timing dependent)</td>
<td>Rate of death or ESRD: 70–80%</td>
<td>Rate of recurrence: 80–90%</td>
</tr>
<tr>
<td>CFHR1/3</td>
<td>Factor HR1, R3</td>
<td>Anti-factor H antibodies</td>
<td>6</td>
<td>Rate of remission: 70–80% (plasma exchange combined with immunosuppression)</td>
<td>Rate of ESRD: 30–40%</td>
<td>Rate of recurrence: 20%</td>
</tr>
<tr>
<td>MCP</td>
<td>Membrane cofactor protein</td>
<td>No surface expression</td>
<td>10–15</td>
<td>No definitive indication for therapy</td>
<td>Rate of death or ESRD: &lt;20%</td>
<td>Rate of recurrence: 15–20%</td>
</tr>
<tr>
<td>CFI</td>
<td>Factor I</td>
<td>Low level or low cofactor activity</td>
<td>4–10</td>
<td>Rate of remission: 30–40%</td>
<td>Rate of death or ESRD: 60–70%</td>
<td>Rate of recurrence: 70–80%</td>
</tr>
<tr>
<td>CF8</td>
<td>Factor B</td>
<td>C3 convertase stabilization</td>
<td>1–2</td>
<td>Rate of remission: 30%</td>
<td>Rate of death or ESRD: 70%</td>
<td>Recurrence in one case</td>
</tr>
<tr>
<td>C3</td>
<td>Complement C3</td>
<td>Resistance to C3b inactivation</td>
<td>5–10</td>
<td>Rate of remission: 40–50%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Rate of recurrence: 40–50%</td>
</tr>
<tr>
<td>THBD</td>
<td>Thrombomodulin</td>
<td>Reduced C3b inactivation</td>
<td>5</td>
<td>Rate of remission: 60%</td>
<td>Rate of death or ESRD: 60%</td>
<td>Recurrence in one case</td>
</tr>
</tbody>
</table>

Table 5. Outcomes after plasma treatment in aHUS patients with mutations in CFH, CFI, C3, THBD, MCP, or CFH autoantibodies and in patients without mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>CFH</th>
<th>CFI</th>
<th>C3</th>
<th>THBD</th>
<th>MCP</th>
<th>CFH Antibodies</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma treated episodes</td>
<td>90 (52 patients)</td>
<td>8 (7 patients)</td>
<td>14 (10 patients)</td>
<td>8 (6 patients)</td>
<td>29 (14 patients)</td>
<td>12 (7 patients)</td>
<td>103 (84 patients)</td>
</tr>
<tr>
<td>Remission</td>
<td>57 (63%)</td>
<td>2 (7%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (57%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (88%)</td>
<td>78 (97%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9 (75%)</td>
<td>71 (69%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Complete remission</td>
<td>5 (5%)</td>
<td>1 (12.5%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (43%)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>5 (62%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26 (90%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (25%)</td>
<td>30 (29%)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Partial remission</td>
<td>52 (58%)</td>
<td>1 (12.5%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (14%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (25%)</td>
<td>2 (7%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (50%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41 (40%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ESRF–death</td>
<td>33 (37%)</td>
<td>6 (75%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (43%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (13%)</td>
<td>1 (3%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (25%)</td>
<td>32 (31%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ESRF</td>
<td>25 (28%)</td>
<td>6 (75%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (43%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>1 (3%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (25%)</td>
<td>31 (30%)</td>
</tr>
<tr>
<td>Death</td>
<td>8 (9%)</td>
<td>—</td>
<td>—</td>
<td>1 (13%)</td>
<td>—</td>
<td>—</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Complete remission is defined as normalization of both hematologic parameters and of renal function (see Table 3). Partial remission is defined as normalization of hematologic parameters with renal sequelae (see Table 3). In this table, we included only the episodes for which information about plasma treatment was available. CFH group includes two patients with CFH mutations and CFH autoantibodies and three patients with the CFH/CFH-R1 hybrid gene.

<sup>a</sup>P < 0.0024 after Bonferroni correction compared with the group with MCP mutations.

<sup>b</sup>P < 0.0024 after Bonferroni correction compared with the group with CFH mutations.
Eculizumab

- **41 patients**  
  - 85% on PLEX/PI  
  - Mean GFR 17ml/min  
  - Eculizumab in single arm  
  - Results at 26 weeks:  
    - 98% normalized platelets  
    - 73% complete TMA response  
    - 54% increased GFR >15ml/min from baseline  
    - Mean increase in GFR 29.3ml/min  
    - 83% (20/24) discontinued hemodialysis  
    - 2 cases of meningococcal infections  
      • Meningitis and sepsis

- **17 patients**  
  Legendre NEJM 2013  
  - 94% on PLEX/PI  
  - Mean GFR 23 ml/min  
  - Eculizumab single arm  
  - Results at 26 weeks:  
    - 82% normalize platelets  
    - 76% normalize hematologic parameters  
    - 47% increased GFR>15ml/min from baseline (increase to 59% at 2 years)  
    - Mean increase GFR 31ml/min  
    - 4/5 discontinue hemodialysis

**REMEMBER to:**  
VACCINATE against Neisseria Meningitidis Serotypes A,C,Y,W135 and meningococcus B (Menactra and Bexsaros)  
Penicillin Prophylaxis
Early Treatment with Eculizumab Improves Renal Outcomes

When compare start of eculizumab in studies <7 days (21 pts) vs >7 days (76 pts)
Mean eGFR change from baseline to 1 year 57 vs 23 ml/min/1.73m²

Vande Walle et al J. Neph 2017

Zuber Nat Rev Neph 2012
Some important thoughts on PLEX in ICU

**Venous Access:**
- Peripheral if possible
- Otherwise need central venous access with dialysis capable catheter

**Safe hemoglobin to start:**
- Hemoglobin ≥ 70g/L
- If 60-69g/L can prime one unit RBC on apheresis device

**Watch electrolytes:**
- Low Ca, K, Mg, PO₄, acidosis, liver dysfunction can exacerbate citrate reaction

**Hemodynamics:**
- Hypovolemia, vasodilation, antihypertensives/diuretics can exacerbate hypotension on apheresis device

**What are you taking out?**
- Medications can be removed by PLEX
  - Specifically: antiseizure medications, antibiotics, IVIG, Rituximab, IV heparin, immunosuppressants

**Please, please, please don’t draw blood work immediately after PLEX**
- Transient dilutional effects on CBC, hypercalcemia from calcium infusions, aPTT/INR increase if just albumin replacement
Some important thoughts on PLEX in ICU

• Adverse events because of PLEX:
  • Citrate reaction
    • Symptoms of hypocalcemia
  • Reaction to plasma
    • Allergic/TRALI
  • Hypotension
  • Citrate systemic anticoagulation
    • Especially if biopsy or surgical procedure being done around time of PLEX
  • Metabolic Alkalosis from plasma metabolism
  • Line infection/thrombosis/air embolism
Thank you