A Practical Approach to the Diagnosis and Management of TTP and Atypical HUS

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Causes of the Syndrome of MAHA and Thrombocytopenia

- MAHA signifies mechanical injury of red blood cells and occurs with
  - Vascular devices (ventricular assist device, prosthetic heart valve, extracorporeal membrane oxygenator)
  - Arteriolar stenosis with abnormal shear stress

- Arteriolar stenosis is associated with at least 5 different types of pathology
  - Fibrin-platelet thrombosis, VWF-platelet thrombosis, thrombotic microangiopathy (TMA), vasculopathy/vasculitis, and intravascular clusters of neoplastic cells

- Arteriolar stenosis is thrombotic in nature in most cases
  - Hence, the syndrome of MAHA and thrombocytopenia
  - In non-thrombotic lesions, thrombocytopenia may result from other processes
Causes of Arteriolar Stenosis with MAHA/Thrombocytopenia

• Fibrin-platelet thrombosis
  – DIC, heparin induced thrombocytopenia, catastrophic antiphospholipid antibody syndrome, HELLP syndrome, arterial aneurysms
• VWF-platelet thrombosis: TTP
• Thrombotic microangiopathy (TMA): non-inflammatory endothelial injury
  – Shiga toxins: Shiga toxin associated HUS
  – Uncontrolled complement activation: AHUS
  – T activation by neuraminidases: pneumococcal or other sepsis
  – Anti-VEGF agents (e.g., bevacizumab)
  – Unknown mechanisms: mitomycin, gemcitabine, cocaine, etc.
  – Other genetic abnormalities: DGKE, MMACHC (cobalamin C disease)
• Vasculopathy/vasculitis: vessel wall injury, with or without inflammation
  – Renal scleroderma
  – Malignant hypertension
  – Small vessel vasculitis (immune complex or ANCA positive)
  – Infection: Rocky Mountain spotted fever, severe C. difficile infection, anthrax
• Metastatic diseases with intravascular clusters of neoplastic cells (tumor cell embolism)
**What Is TTP?**

- A disorder with propensity to arteriolar thrombosis due to severe deficiency of ADAMTS13, resulting from genetic mutations or autoimmune inhibitors
- The mechanistic definition of TTP includes atypical presentations of the disease without thrombocytopenia and/or MAHA
- Modes of presentation
  - Thrombocytopenia and MAHA, with or without organ dysfunction
    - Brain dysfunction is the most common cause of symptoms and signs
      - Focal deficits, visual defects, confusion, seizures, coma
    - Abdominal pain, with or without pancreatitis
    - Myocardial injury, heart failure, arrhythmias, cardiac arrest
    - Kidney: hematuria
  - Thrombocytopenia, no MAHA, with or without organ dysfunction
    - Often mistaken to be ITP
  - Stroke, TIA or myocardial infarction, without MAHA and/or thrombocytopenia
  - MAHA and thrombocytosis (smoldering TTP)
  - Subclinical platelet consumption, without MAHA and thrombocytopenia
    - Platelet count is increased with plasma infusion
    - A risk factor of thrombotic complications in patients with congenital TTP
    - Indication of maintenance plasma therapy for congenital TTP
## Causes of Severe ADAMTS13 Deficiency

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<tr>
<th>Type of deficiency</th>
<th>Causes</th>
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| Acquired           | Inhibitory antibodies  
                     Ticlopidine: 200x - 300x  
                     HIV infection: 30x - 40x  
                     Female gender: 2x - 3x  
                     Most cases are idiopathic  
                     Dysregulation of autoimmunity? |
| Hereditary         | Mutations of ADAMTS13 (autosomal recessive) |
| Others             | ADAMTS13 activity may be diminished in vitro in plasma samples from patients with various pathologic conditions such as DIC, sepsis, liver cirrhosis, multi-organ failure, and HELLP  
                     Immediate centrifugation and freezing of plasma are critical to avoid spurious ADAMTS13 deficiency.  
                     ADAMTS13 activity may also be lost after repeated freezing and thawing or long storage above -70°C |
Pathophysiology of TTP

Severe ADAMTS13 deficiency (mutations or inhibitory Ab)

VWF becomes activated by shear stress in the circulation

Arteriolar and capillary VWF-platelet thrombosis

- Ischemia
- Platelet consumption
- Abnormal shear stress

Organ dysfunction (Brain, kidney, heart, etc.)
Thrombocytopenia
Microangiopathic hemolytic anemia

- Decreasing platelet count or thrombocytopenia is often the leading abnormality during the development of TTP.
- Occasionally neurological deficit may present before thrombocytopenia ensues, if a microthrombus happens to affect a vital area of the brain.
- Thrombosis of a large vessel may occur and cause stroke or MI if a microthrombus happens to affect the vasa vasorum of a large artery, resulting in endothelial injury and thrombosis in the vessel.
When to Order ADAMTS13 Tests and How to Interpret the Results

• At presentation, when TTP is suspected
  – ADAMTS13 <10% is diagnostic of TTP

• When the increase of the platelet count stalls during the course of plasma therapy for TTP
  – ADAMTS13 >10%: search for another cause of thrombocytopenia
  – Conditions that have been found to cause thrombocytopenia in TTP patients undergoing plasma therapy: catheter sepsis, heparin induced thrombocytopenia, HIV disease, active lupus, and ITP

• At the time of clinical remission and during the first 4-8 weeks after remission
  – ADAMTS13 often is unstable for several weeks; weekly monitoring is often necessary
  – ADAMTS13 <30% or trending downward that level is a risk factor for early relapse and therefore is an indication for prophylactic rituximab

• During remission
  – Biweekly or monthly ADAMTS13 monitoring
  – A downward trend toward 30% is an indication for prophylactic rituximab
### Indications of Rituximab Therapy for TTP

- With prompt plasma exchange for acute episodes, the mortality should be ≤10%
- Current challenges: need of plasma exchange, early death (<10-14 days), late death, early relapse (<4-8 weeks) and late relapse
- With rituximab it is possible to alleviate some of the problems

<table>
<thead>
<tr>
<th>Time</th>
<th>Comments</th>
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<tbody>
<tr>
<td>During plasma exchange for acute TTP</td>
<td>May potentially decrease the risk of late TTP death (after 10-14 days), the numbers of PEx to remission, and the risk of early relapse Efficacy has not been convincingly established</td>
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<tr>
<td>At or soon after remission</td>
<td>Monitoring of ADAMTS13 weekly to biweekly Prophylactic rituximab for ADAMTS13 &lt;30% or trending downward to that level</td>
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<tr>
<td>During remission</td>
<td>Monitoring of ADAMTS13 biweekly to monthly Prophylactic rituximab for ADAMTS13 activity trending toward 30%</td>
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### Other Modalities of Treatment for TTP

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<tr>
<th>Modality</th>
<th>Mechanism of action and comments</th>
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| **Corticosteroids, cyclophosphamide, vincristine, azathioprine** | Immunosuppression  
Reported usage: acute, persistent or relapsing TTP  
Questionable efficacy in lowering ADAMTS13 inhibitors |
| **Aspirin, dipyridamole, ticlopidine** | Anti-platelet function  
Questionable efficacy in blocking VWF-platelet thrombosis |
| **N-acetylcysteine** | Reduces the size of VWF multimers  
Reported usage: refractory TTP  
Effective drug concentration is difficult to reach in vivo  
Treatment failure is not uncommon |
| **Calcineurin inhibitors (e.g., cyclosporine A)** | Cellular immunosuppression  
Reported usage: prevention of relapse  
Slow action, side effects, treatment failure |
| **Proteosome inhibitors (e.g., bortezomib)** | Promotes depletion of long lasting plasma cells  
Reported usage: no or inadequate response to rituximab |
| **Anti-VWF Ab (e.g., caplacizumab)** | Fast blocker of VWF-platelet thrombosis  
Decreases the numbers of plasma exchange to achieve remission  
Has potential to decrease the risk of early and late TTP death  
Very high risk of relapse if treatment is discontinued before ADAMTS13 is >10% |
What is Atypical HUS (AHUS)?

- A disorder with propensity to thrombotic microangiopathy (TMA) due to defective regulation of the alternative complement pathway
- AHUS is different from TTP not only in pathogenesis but also in pathology
  - TTP: arteriolar and capillary VWF-platelet thrombosis due to ADAMTS13 deficiency
  - AHUS: TMA, with endothelial injury and sub-endothelial expansion due to edema or fibrous proliferation; thrombosis is secondary endothelial disruption and not invariably present
  - AHUS is only one of at least six groups of disorders associated with TMA (slide 3)
- The mechanistically defined AHUS encompasses patients without renal failure, MAHA and/or thrombocytopenia
- Modes of presentation
  - MAHA, thrombocytopenia and renal function impairment
  - Renal function impairment, without MAHA and/or thrombocytopenia
  - Hypertension, without MAHA, thrombocytopenia and/or renal impairment
  - No symptoms and normal laboratory test results
    - Propensity to TMA upon encounter with triggers of complement activation (e.g., intravenous radiographic contrast agents, vascular catheters, certain infections)
Pathogenesis and Pathophysiology of AHUS

Mutation of complement regulators (CFH, CD46, CFI, THBD)
Or activators (C3, CFB); CFH Ab

Spontaneous or triggered

Uncontrolled complement activation

C5b-9 (MAC)

EC injury (endothelial swelling, disruption; subendothelial expansion)

C3a, C5a

Histamine release

↑Vascular permeability

• Effusions
• Extra-renal interstitial edema & organ dysfunction

Platelet consumption

Thrombocytopenia

MAHA

HTN

Renal function impairment

↑Shear stress

↑Renin

Arteriolar/arterial stenosis

Glomerular injury

Thrombotic

Non-thrombotic

Renin

HTN

Renal function impairment

MAHA

Effusions

Extra-renal interstitial edema & organ dysfunction
Complications of AHUS

• The complications of AHUS may be classified in 5 groups
  • Renal function impairment, MAHA, thrombocytopenia, hypertension and extra-renal abnormalities
  • Extra-renal complications, primarily due to abnormal vascular permeability, are often neglected yet are the most common cause of sudden death with AHUS
    • Brain: headache, dizziness, confusion, seizures, and/or coma; posterior reversible encephalopathy syndrome (PRES) due to interstitial edema; brain stem herniation
    • Eye: visual defects, retinal exudates or vascular occlusion
    • Chest: dyspnea, cough, chest pain, bronchial wall edema and thickening, pleural effusion, alveolar edema, respiratory failure
    • Heart: chest pain; pericardial effusion; cardiac failure, arrhythmia or arrest
    • Abdomen: abdominal pain; anorexia, nausea, vomiting; ascites; interstitial edema of intestinal wall, mesentery and/or pancreas; thrombosis of mesenteric vessels
    • Soft tissues: edematous swelling of face, body and/or extremities
Evaluating the Complications of AHUS

• The five groups of complications differ in pathogenesis and often are not concordant during the course of the disease, e.g.,
  – Progressive renal failure or worsening neurologic functions with stable platelet count and/or hemolysis
  – Headache, dizziness, anorexia with stable lab results
  – Severe hypertension with no or minimal renal failure, MAHA and/or thrombocytopenia

• All groups of complications should be carefully evaluated and included in the assessment of disease activity
Anti-Complement Therapy for AHUS

- Patients of AHUS are at risk of sudden death from brain edema and herniation, cardiac arrhythmia or arrest
- Anti-complement therapy should be immediately instituted when AHUS is the presumptive diagnosis, especially for patients with complications of abnormal vascular permeability
- Anti-complement therapy may stabilize or improve renal function even in patients with advanced or long-standing renal failure.
- With anti-complement therapy, resolution of thrombocytopenia is expected by day 7 and abnormal vascular permeability should improve or resolve by day 14 after the first dose, unless the patient continues to be on plasma exchange or has another disease process
- Recovery of renal function may not be apparent for months; it may slowly continue for several months to over a year
  - Anti-complement therapy should not be given up too early
  - Patients should not be rushed to renal transplantation
- Anti-complement therapy may be cautiously tapered off for a patient with good recovery and has no symptoms and signs of AHUS
  - The treatment interval is gradually increased under careful monitoring
  - The patient should be aware that symptoms such as dizziness, anorexia, nausea, abdominal pain, difficult breathing, chest pain, etc. may be early indicators of disease activity
  - The patient should have immediate access to expert evaluation for any suspicious symptoms or signs of disease activity.
Differential Diagnosis of MAHA and Thrombocytopenia - An Overview

• TTP and AHUS together account for the majority but not all of the cases presenting with MAHA and thrombocytopenia (70% - 80%)

• Normal or minimally impaired renal function favors the diagnosis of TTP

• Prominent renal function impairment (maximal Cr >2.5 mg/mL) favors the diagnosis of AHUS

• Exceptions to these rules
  – TTP may present with renal failure
    ▪ Occasionally a patient has a concurrent disorder such as STX-HUS, AHUS, or anti-GBM nephropathy that causes renal failure.
    ▪ Congenital TTP may be associated with acute and chronic renal failure
  – AHUS may present with mild renal impairment

• An ADAMTS13-based systemic approach is essential for correct differential diagnosis
A Systemic Approach to the Differential Diagnosis of MAHA and Thrombocytopenia

- For all patients, history, physical examination and these laboratory tests are indicated
  - ADAMTS13, DIC panel, ANA, lupus anticoagulants, anti-cardiolipin Ab, β2-GP1 Ab, stool Shiga toxin assay
- ADAMTS13 <10% confirms the diagnosis of TTP
  - Positive ADAMTS13 inhibitor result is diagnostic of acquired TTP. A negative result does not exclude acquired TTP
  - Acquired TTP is the diagnosis if
    - ADAMTS13 is ≥ 15% during remission without plasma therapy, or
    - Increase of ADAMTS13 is less than expected with plasma therapy
  - Congenital or hereditary TTP is the likely diagnosis if
    - The disease first presents during infancy
    - Partial deficiency in both parents or all children, or one or more siblings with inhibitor-negative TTP
    - ADAMTS13 level is increased as expected with plasma therapy
- TTP is excluded for ADAMTS13 >20% while platelet count is decreasing or thrombocytopenia not improving
  - Initial history and lab test results may point toward other causes such as HELLP, HIT, DIC, drugs, STX-HUS, pneumococcal sepsis, autoimmune disorders, etc.
- AHUS is the presumptive diagnosis in patients renal impairment and no comorbidity
  - Molecular testing is performed to confirm AHUS. Negative results do not exclude AHUS
  - Empiric eculizumab is indicated for presumptive AHUS without waiting for molecular confirmation
    - Resolution of thrombocytopenia within one week or of abnormal vascular permeability within two weeks support AHUS
    - AHUS is excluded when such responses are not achieved, unless the patient is on plasma exchange or has another cause of thrombocytopenia
  - Laboratory testing for DGKE mutations and cobalamin C disease is indicated
- ADAMTS13 between 10% and 20%: TTP after receiving blood products, TTP undergoing spontaneous recovery, or a non-TTP disorder with unusually low ADAMTS13
## Differential Diagnosis of MAHA/thrombocytopenia in Patients with Comorbidities (after TTP Is Excluded)

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<tr>
<th>Comorbidity</th>
<th>Differential diagnosis</th>
<th>Comments</th>
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| Autoimmunity (ANA, LA, anti-cardiolipin) | • AHUS  
• Vasculitis/vasculopathy  
• Fibrin-platelet thrombosis | Biopsy is often needed for differential diagnosis                        |
| Hematopoietic stem cell therapy    | • Fungemia/viremia  
• Myeloablative drugs  
• Calcineurin inhibitors  
• AHUS | Exclude or treat infection  
Adjust anti-GVHD regimen  
Empiric anti-complement after infection and anti-GVHD drugs are excluded |
| Solid organ transplant             | • Fungemia/viremia  
• Anti-rejection drugs  
• Severe rejection reaction  
• AHUS | Exclude or treat infection  
Adjust anti-rejection regimen  
Biopsy as indicated for severe rejection  
Empiric anti-complement therapy |
| ‘Malignant hypertension’           | • Severe hypertension causing endothelial injury  
• AHUS with severe hypertension | Empiric anti-complement therapy when controlling BP is difficult or ineffective |
| Pregnancy                          | • Preeclampsia/HELLP  
• AHUS | Empiric anti-complement therapy, especially for prominent renal failure or onset/persistence/worsening after delivery |
When TTP or AHUS Should Be Suspected in Patients without MAHA and/or Thrombocytopenia

• TTP
  – Thrombocytopenia or ‘ITP’
    • Especially if the patient has symptoms or signs that are unusual for ITP (e.g., headache without hemorrhage, non-hemorrhagic stroke)
  – Stroke, TIA or acute coronary syndrome in a patient with a history of TTP
  – Stroke, TIA or acute coronary syndrome with otherwise unexplained thrombocytopenia
  – Stroke, TIA, or acute coronary syndrome in a young person without risk factors

• AHUS
  – Progressive renal impairment in a patient with a history of AHUS
  – Hypertension or ‘malignant hypertension’ that is severe but unstable and difficult to control
  – Candidates of renal transplantation for advanced renal failure of unknown etiology
  – ‘Preeclampsia/HELLP’ with prominent renal failure
  – ‘Preeclampsia/HELLP’ with onset, persistence or worsening after delivery
  – Family history of AHUS (autosomal dominant transmission)