Identifying Atypical Hemolytic Uremic Syndrome in the Intensive Care Unit Setting

A Guide To Differential Diagnosis
Identifying atypical-HUS as the cause of thrombotic microangiopathy (TMA) in the ICU setting is essential for an accurate and timely diagnosis and optimal management decisions.

1. **Consider**
   - Full medical history
   - To identify potential trigger
   - Such as previous TMA, pregnancy, prior malignancy, drug use

2. **Consider**
   - Clinical picture, microbiologic screening, and assessment of coagulation screen
   - To rule out
   - DIC and sepsis

3. **Consider**
   - ADAMTS13 activity test, a Shiga toxin test, and assessment of homocysteine and methylmalonic acid in plasma
   - To rule out
   - TTP, STEC-HUS, and cobalamin C deficiency, respectively

If TMA persists on specific treatment of the associated condition, consider a diagnosis of atypical-HUS.

TMA due to atypical-HUS

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*Prior to plasma exchange/plasma infusion (PE/PI) for an accurate baseline reading, though it may be conducted afterward.*
Case Study: Adult Patient in ICU

**Patient overview**
- 62-year-old Japanese male; height: 165 cm; weight: 99 kg (218 lb)
- Presented to local hospital after 1 month of mucous and bloody stool and 2 weeks of worsening abdominal pain
- Lab results showed leukocytosis, thrombocytopenia, and elevated blood urea nitrogen and serum creatinine

**Clinical presentation and management**

<table>
<thead>
<tr>
<th>1 month of mucous and bloody stool and 2 weeks of worsening abdominal pain</th>
<th>Condition deteriorated despite treatment; patient transferred to ICU</th>
<th>Lower GI endoscopy showed no evidence of colitis or inflammation. Thrombocytopenia persisted. Patient experienced respiratory distress and pleural effusion</th>
<th>Thrombocytopenia persisted after 8 TPE sessions</th>
</tr>
</thead>
</table>

**Laboratory Values**

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Normal values</th>
<th>ICU day 1</th>
<th>ICU days 9-11</th>
<th>ICU day 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, x 10^9/L</td>
<td>3.5-10.5</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.0-0.8</td>
<td>23.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procalcitonin, ng/mL</td>
<td>≤0.15</td>
<td>8.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count, x 10^9/L</td>
<td>150-350</td>
<td>38</td>
<td>21</td>
<td>59</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>100</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrin degradation product level, μg/mL</td>
<td>&lt;5</td>
<td>53.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH, IU/L</td>
<td>60-100</td>
<td>392</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate transaminase, IU/L</td>
<td>0-35</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine transaminase, IU/L</td>
<td>0-35</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.3-1.2</td>
<td>6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct bilirubin, mg/dL</td>
<td>0.3</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>8-20</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.7-1.3</td>
<td>2.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic acid, mg/dL</td>
<td>6-16</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Complement measurements**

<table>
<thead>
<tr>
<th>DATE OF TEST</th>
<th>Normal values</th>
<th>ICU day 1</th>
<th>ICU days 9-11</th>
<th>ICU day 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH50, U/mL</td>
<td>30-50</td>
<td>40.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3, mg/dL</td>
<td>65-135</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4, mg/dL</td>
<td>13-35</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Differential diagnosis evaluation**

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Normal values</th>
<th>ICU day 1</th>
<th>ICU days 9-11</th>
<th>ICU day 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schistocytes</td>
<td>Negative</td>
<td>Negative</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Enterococcus sp.</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corynebacterium striatum</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAMTS13 activity</td>
<td>&gt;10%</td>
<td></td>
<td>25.1</td>
<td></td>
</tr>
<tr>
<td>STEC-HUS</td>
<td>Negative</td>
<td></td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

**Differential Diagnosis**

- A final diagnosis of atypical-HUS was made based on ruling out other potential causes of TMA (STEC-HUS, TTP)

Patient case is hypothetical.
Case Study: Pediatric Patient in ICU

Patient overview

- 5-year-old Caucasian female; height: 110 cm; weight: 18 kg (40 lb)
- Presented to the department of pediatric nephrology with vomiting, petechiae on the lower extremities, yellowish sclera, systolic heart murmur, weakness, catarrhal infection, and oliguria present for 2 days
- Upper airway infection without diarrhea for 3 days
- Lab results consistent with hemolytic anemia, thrombocytopenia, acute renal failure, elevated LDH activity, proteinuria, and hematuria

Clinical presentation and management

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Normal values</th>
<th>At presentation</th>
<th>1 week after presentation</th>
<th>11 months after presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.4-14.3</td>
<td>9.7</td>
<td>11.0</td>
<td>12.7</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>34-42</td>
<td>28.9</td>
<td>32.4</td>
<td>38.8</td>
</tr>
<tr>
<td>White blood cells × 10^3/L</td>
<td>4.4-12.9</td>
<td>6.0</td>
<td>8.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Platelets × 10^9/L</td>
<td>187-445</td>
<td>15</td>
<td>332</td>
<td>310</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>7-20</td>
<td>84.01</td>
<td>13.16</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.12-1.06</td>
<td>1.38</td>
<td>0.64</td>
<td>0.43</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>145-345</td>
<td>7669</td>
<td>1682</td>
<td>627</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>&lt;1.0</td>
<td>12.4</td>
<td>9.6</td>
<td>&lt;5.0</td>
</tr>
</tbody>
</table>

Complement measurements

- C50/mL 48-103 47 56
- C3, g/L 0.9-1.8 0.87 1.0
- C4, g/L 0.15-0.55 0.10 0.13

Differential diagnosis evaluation

- Mycoplasma pneumoniae IgM Negative Positive
- Coombs test Negative
- STEC test Negative
- Influenza A Negative
- ADAMTS13 >10%

Differential Diagnosis

- A diagnosis of atypical-HUS was made based on
  - The presence of laboratory findings consistent with atypical-HUS
  - ADAMTS13 activity level that was >10%, ruling out TTP as a cause of TMA
  - Genetic analyses indicating mutations in the complement pathway

Patient case is hypothetical.
Clinical recognition of thrombotic microangiopathy (TMA) requires documentation of microangiopathic hemolysis (confirmed by any one of the following labs: fragmented red blood cells or schistocytes on peripheral blood smear, low haptoglobin levels, elevated lactate dehydrogenase (LDH), decline in baseline hemoglobin), thrombocytopenia, and clinical involvement of at least 1 organ system, the most common sites being the central nervous system, kidneys, and gastrointestinal tract. Triggers are conditions that can activate complement and may unmask atypical-HUS. It is imperative to treat the trigger, but if the signs and symptoms of TMA do not resolve, consider a diagnosis of unmasked atypical-HUS.

### Differential Diagnosis of Atypical-HUS

- Hemolytic uremic syndrome; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy
- Pregnancy-postpartum
- Autoimmune disease
- Malignant hypertension
- Infection
- Transplant (solid organ, HSCT)

### Microangiopathic hemolysis (evidence of any 1 of the below)

<table>
<thead>
<tr>
<th>DATE OF TEST</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Schistocytes (present)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH (elevated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Haptoglobin (low)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (low)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Thrombocytopenia

<table>
<thead>
<tr>
<th>DATE OF TEST</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (&lt;150,000/mm³ or &gt;25% decrease from baseline)</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

### Organ involvement (≥1 organ system, check which apply)

- CNS (Confusion, seizures, stroke)
- GI (Diarrhea, nausea, vomiting abdominal pain)
- CV (MI, hypertension, arterial stenosis)
- Renal (Decreased eGFR, elevated creatinine, abnormal urinalysis)
- Pulmonary (Dyspnea, pulmonary hemorrhage or edema)
- Visual (Blurred vision, retinal vessel or ocular hemorrhage)

### Triggers (can “unmask” atypical-HUS, may or may not be present) (check which apply)

- Infection
- Pregnancy/post-partum (HELLP, pre-eclampsia)
- Transplant (solid organ, HSCT)
- Malignant hypertension
- Autoimmune disease

If a TMA is confirmed, it is important to order an ADAMTS13 activity test and determine the cause:

- Take a thorough medical history
- Order tests to rule out TTP, STEC-HUS, DIC
  - Note that if baseline platelet values are >30 x 10⁹/L or if serum creatinine is >1.7 to 2.3 mg/dL, a diagnosis of TTP is almost eliminated
- Involve specialists in determining diagnosis such as hematologists or nephrologists

- ADAMTS13 activity test ordered
Differential Diagnosis of Atypical-HUS<sup>9,10,12,13</sup>

**Common Signs and Symptoms**

- **Neurological symptoms**
  - Confusion and/or
  - Seizures and/or
  - Stroke and/or
  - Other cerebral abnormalities

- **Renal impairment**
  - Elevated creatinine level and/or
  - Decreased eGFR and/or
  - Elevated blood pressure and/or
  - Abnormal urinalysis results

- **GI symptoms**
  - Diarrhea ± blood and/or
  - Nausea/vomiting and/or
  - Abdominal pain and/or
  - Gastroenteritis/pancreatitis

**Other Signs and Symptoms**

- **CV symptoms**
  - MI and/or
  - Hypertension and/or
  - Arterial stenosis and/or
  - Peripheral gangrene

- **Pulmonary symptoms**
  - Dyspnea and/or
  - Pulmonary hemorrhage and/or
  - Pulmonary edema

- **Visual symptoms**
  - Pain and blurred vision and/or
  - Retinal vessel occlusion and/or
  - Ocular hemorrhage

**Checklist to confirm TMA**

- Mark test result in column below each date

**Evaluate ADAMTS13 activity<sup>a</sup> and Shiga toxin/EHEC test<sup>b</sup>**

While ADAMTS13 results are awaited, a platelet count >30 × 10<sup>9</sup>/L and/or sCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

- ≤5%<sup>c</sup> ADAMTS13 activity
- >5% ADAMTS13 activity
- Shiga toxin/EHEC positive

**TMA can also manifest in the presence of clinical conditions such as the following**

- Pregnancy-postpartum
- Malignant/severe hypertension
- Solid organ transplantation
- Autoimmune disease (eg, SLE, scleroderma)
- Hematopoietic stem cell transplantation

<sup>a</sup> Ideally draw ADAMTS13 activity test prior to initiating plasma exchange/plasma infusion (PE/PI).  
<sup>b</sup> Shiga toxin/EHEC test is warranted with history/presence of GI symptoms.  
<sup>c</sup> Range found in published literature is <5%-10%.

**ADAMTS13**, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; **HUS**, hemolytic uremic syndrome; **CV**, cardiovascular; **eGFR**, estimated glomerular filtration rate; **EHEC**, enterohemorrhagic *Escherichia coli*; **GI**, gastrointestinal; **MI**, myocardial infarction; **sCr**, serum creatinine; **STEC-HUS**, Shiga toxin–producing *Escherichia coli*–hemolytic uremic syndrome; **SLE**, systemic lupus erythematosus; **TMA**, thrombotic microangiopathy; **TTP**, thrombotic thrombocytopenic purpura.
Differential Diagnosis: Identifying Atypical-HUS in the ICU Setting

- Thrombotic microangiopathy (TMA) is a serious medical condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury. The critical nature of acute TMA means that a high proportion of patients may be admitted to the ICU at presentation.

- Due to the severity of the progression of atypical-HUS and other TMAs, a suspected diagnosis should be treated as a medical emergency.

- Appropriate laboratory tests should be ordered immediately to rule out causes of TMA including DIC, STEC-HUS, and TTP.

- Although plasma exchange is not an effective long-term management strategy for atypical-HUS, it may be necessary to implement while laboratory results are being determined and a diagnosis is being confirmed.

- It is critical to recognize that a patient may have a complete or near-complete remission on plasma exchange alone, yet go on to develop ESRD or die.

- According to the American Society for Apheresis, plasma exchange in atypical-HUS receives a weak recommendation, with low-quality or very low-quality evidence.

- In lieu of ADAMTS13 results, a platelet count >30 x 10^9/L and/or serum creatinine >1.7 to 2.3 mg/dL almost eliminates a diagnosis of TTP.

Multiple studies on a total of 806 patients with TMA have demonstrated that baseline values of serum creatinine and platelets at clinical presentation can rapidly and efficiently distinguish between sufficient and severely deficient ADAMTS13 activity.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Serum creatinine level</th>
<th>Platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bentley 2010 (N=110)</td>
<td>P=0.0207</td>
<td>P=0.0034</td>
</tr>
<tr>
<td>Cataland 2012 (N=54)</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Coppo 2010 (N=214)</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Kremer Hovinga 2010 (N=261)</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Shah 2013 (N=60)</td>
<td>P=0.0003</td>
<td>P=0.0001</td>
</tr>
<tr>
<td>George 2010 (N=107)</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

ADAMTS13 deficiency defined as ADAMTS13 activity: <5% (mild deficiency =5%-20%) (Coppo 2010), <10% (Cataland 2012, Kremer Hovinga 2010, George 2010), <15% (Bentley 2010); <10% (Shah 2013). ADAMTS13 assays generally have a sensitivity of 5%-10%. “Severely deficient” ADAMTS13 activity is typically defined as <5%.

Additional clinical parameters that may predict ADAMTS13 activity include indirect bilirubin, reticulocytes, estimated glomerular filtration rate, antinuclear antibodies, acute renal failure, neurological features, and undetectable haptoglobin.

- Atypical-HUS is a disease caused by dysregulation of the alternative pathway of the complement system, leading to excessive complement activation and TMA.

- Atypical-HUS may be triggered by conditions that activate complement such as organ transplantation, infections, malignancy, pregnancy, autoimmune disorders.

- Persistence of TMA despite treatment of associated conditions may suggest atypical-HUS.
Atypical-HUS is a serious disease caused by dysregulation of the alternative pathway of the complement system, leading to excessive complement activation and TMA

Given the critical nature of acute TMA, many patients may be admitted to the ICU at presentation.

If TMA is suspected, consider consulting a multidisciplinary team of specialists in the diagnostic process. Follow the pathway to reach a diagnosis.

It is important to diagnose atypical-HUS promptly in patients admitted to the ICU in order to reduce the risk of irreversible organ damage or death.

References