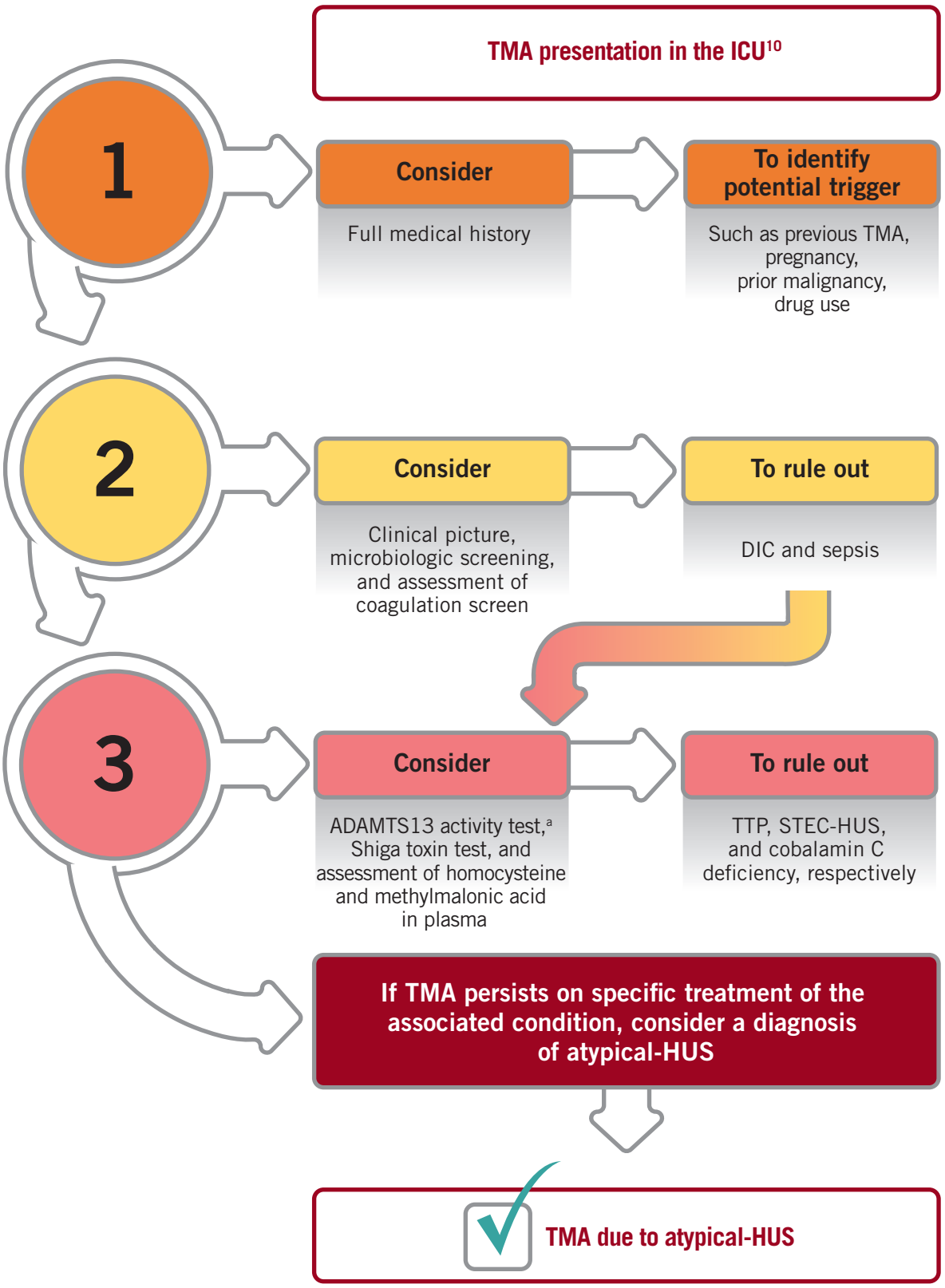
Identifying Atypical Hemolytic Uremic Syndrome in the Intensive Care Unit Setting

A Guide To Differential Diagnosis

Identifying Atypical Hemolytic Uremic Syndrome in the Intensive Care Unit Setting

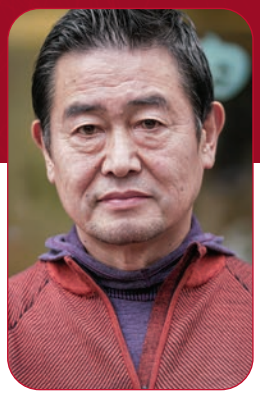
Important Considerations for a Differential Diagnosis

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



[a]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[1-5]



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

At presentation	ICU day 1	ICU days 9-11	ICU day 26
1 month of mucous and bloody stool and 2 weeks of worsening abdominal pain	Condition deteriorated despite treatment; patient transferred to ICU	Lower GI endoscopy showed no evidence of colitis or inflammation. Thrombocytopenia persisted. Patient experienced respiratory distress and pleural effusion	Thrombocytopenia persisted after 8 TPE sessions
Diagnosis: sepsis secondary to intra-abdominal infection; broad-spectrum antimicrobial therapy initiated	Diagnosis: severe bacterial enteritis	Revised diagnosis: TMA Therapeutic plasma exchange (TPE) initiated, ADAMTS13 activity test ordered	Negative for STEC-HUS; normal ADAMTS13 activity, ruling out TTP Final diagnosis: atypical-HUS

Laboratory Values

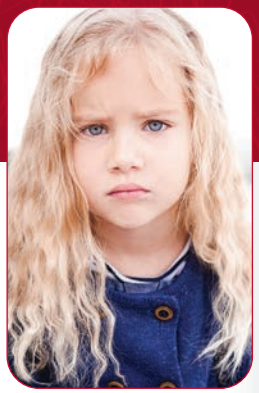
Laboratory Tests	Normal values	ICU day 1	ICU days 9-11	ICU day 26
White blood cell count, × 10^9/L	3.5-10.5	12		
C-reactive protein, mg/dL	0.0-0.8	23.9		
Procalcitonin, ng/mL	≤0.15	8.92		
Platelet count, × 10^9/L	150-350	38	21	59
Prothrombin time, %	100	41		
Fibrin degradation product level, µg/mL	<5	53.1		
LDH, IU/L	60-100	392		
Aspartate transaminase, IU/L	0-35	50		
Alanine transaminase, IU/L	0-35	17		
Total bilirubin, mg/dL	0.3-1.2	6.2		
Direct bilirubin, mg/dL	0-0.3	4.6		
BUN, mg/dL	8-20	92		
Serum creatinine, mg/dL	0.7-1.3	2.09		
Lactic acid, mg/dL	6-16	4		
Complement measurements				
CH50, U/mL	30-50	40.6		
C3, mg/dL	65-135	85		
C4, mg/dL	13-35	23		
Differential diagnosis evaluation				
Anemia	Negative	Negative		
Schistocytes	Negative	Negative	0.5	
Enterococcus sp.	Negative	Positive		
Corynebacterium striatum	Negative	Positive		
ADAMTS13 activity	>10%			25.1
STEC-HUS	Negative			Negative

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[6-8]



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

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	Improvement in LDH and renal and hematologic findings	Good clinical condition
At presentation	**1 week after presentation**	**11 months after presentation**
Admitted to ICU Diagnosis: Mycoplasma pneumonia with TMA Treatment with clarithromycin therapy, fresh-frozen plasma on days 3, 4, 5, and 6, and renal replacement therapy with peritoneal dialysis on days 2, 3, 4, and 5	Differential: negative Coombs and STEC-HUS tests, normal ADAMTS13 activity Diagnosis: atypical-HUS	Genetic analysis revealed mutations in the complement pathway

Laboratory Values

Laboratory Tests	Normal values	At presentation	1 week after presentation	11 months after presentation
Hemoglobin, g/dL	11.4-14.3	9.7	11.0	12.7
Hematocrit, %	34-42	28.9	32.4	38.8
White blood cells × 10^9/L	4.4-12.9	6.0	8.9	6.2
Platelets × 10^9/L	187-445	15	332	310
BUN, mg/dL	7-20	84.01		13.16
Serum creatinine, mg/dL	0.12-1.06	1.38	0.64	0.43
LDH, U/L	145-345	7669	1682	627
CRP, mg/L	<1.0	12.4	9.6	<5.0
Complement measurements				
CH50/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		Negative	
STEC test	Negative		Negative	
Influenza A	Negative		Negative	
ADAMTS13	>10%		Normal	

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.

Checklist to confirm TMA

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.[9] 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.[9]

Microangiopathic hemolysis (evidence of any 1 of the below)

Mark test result in column below each date

DATE OF TEST				
Schistocytes (present)				
LDH (elevated)				
Haptoglobin (low)				
Hemoglobin (low)				

Thrombocytopenia

Mark test result in column below each date

DATE OF TEST				
Platelet count (<150,000/mm^3 or >25% decrease from baseline)				

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:

☐ **ADAMTS13 activity test ordered**

- Take a thorough medical history[10]
- Order tests to rule out TTP, STEC-HUS, DIC[9,10]
  - Note that if baseline platelet values are >30 x 10^9/L or if serum creatinine is >1.7 to 2.3 mg/dL, a diagnosis of TTP is almost eliminated[9]
- Involve specialists in determining diagnosis such as hematologists or nephrologists[11]

Differential Diagnosis of Atypical-HUS[9,10,12,13]

Thrombocytopenia
Platelet count <150 × 10^9/L or >25% decrease from baseline

AND

Microangiopathic hemolysis
Schistocytes and/or
Elevated LDH and/or
Decreased haptoglobin and/or
Decreased hemoglobin

Plus 1 or more of the following

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

Evaluate ADAMTS13 activity[a] and Shiga toxin/EHEC test[b]

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

≤5%[c] ADAMTS13 activity	>5% ADAMTS13 activity	Shiga toxin/EHEC positive
TTP	Atypical-HUS	STEC-HUS

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

[a]Ideally draw ADAMTS13 activity test prior to initiating plasma exchange/plasma infusion (PE/PI). [b]Shiga toxin/EHEC test is warranted with history/presence of GI symptoms. [c]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[10]
- The critical nature of acute TMA means that a high proportion of patients may be admitted to the ICU at presentation[10]
  - According to a meta-analysis, physicians in the ICU see an average of three patients with TMA per year, many of whom are not diagnosed at the time of admission[10]
- Due to the severity of the progression of atypical-HUS and other TMAs, a suspected diagnosis should be treated as a medical emergency[10]
  - Appropriate laboratory tests should be ordered immediately to rule out causes of TMA including DIC, STEC-HUS, and TTP[10]
    - To rule out TTP, an ADAMTS13 activity level (not antibody) test should be ordered[9]
  - 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[9,10]
    - 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[9]
    - According to the American Society for Apheresis, plasma exchange in atypical-HUS receives a weak recommendation, with low-quality or very low-quality evidence[14]
- In lieu of ADAMTS13 results, a platelet count >30 × 10^9/L and/or serum creatinine >1.7 to 2.3 mg/dL almost eliminates a diagnosis of TTP[9]

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[15-20,a]

Serum creatinine level and platelet count show statistical significance in predicting ADAMTS13 activity[a]

	Association with severe ADAMTS13 deficiency: *P* value	
Authors	**Serum creatinine level**	**Platelet count**
Bentley 2010 (N=110)[15]	*P*=0.0207	*P*=0.0034
Cataland 2012 (N=54)[16]	*P*<0.0001	*P*<0.0001
Coppo 2010 (N=214)[17]	*P*<0.0001	*P*<0.0001
Kremer Hovinga 2010 (N=261)[18]	*P*<0.001	*P*<0.001
Shah 2013 (N=60)[19]	*P*=0.0003	*P*=0.0001
George 2010 (N=107)[20]	*P*<0.001	*P*<0.001

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%.

[a]Additional clinical parameters that may predict ADAMTS13 activity include indirect bilirubin,[15] reticulocytes,[15,17] estimated glomerular filtration rate,[17] antinuclear antibodies,[17] acute renal failure,[18,20] neurological features,[19] and undetectable haptoglobin.[19]

- Atypical-HUS is a disease caused by dysregulation of the alternative pathway of the complement system, leading to excessive complement activation and TMA[13,21]
  - Atypical-HUS may be triggered by conditions that activate complement such as organ transplantation, infections, malignancy, pregnancy, autoimmune disorders[9]
  - Persistence of TMA despite treatment of associated conditions may suggest atypical-HUS[10]

Atypical-HUS is a serious disease caused by dysregulation of the alternative pathway of the complement system, leading to excessive complement activation and TMA[13,21]

Given the critical nature of acute TMA, many patients may be admitted to the ICU at presentation[10]

If TMA is suspected, consider consulting a multidisciplinary team of specialists in the diagnostic process.[11] Follow the pathway to reach a diagnosis[9]

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[10]

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