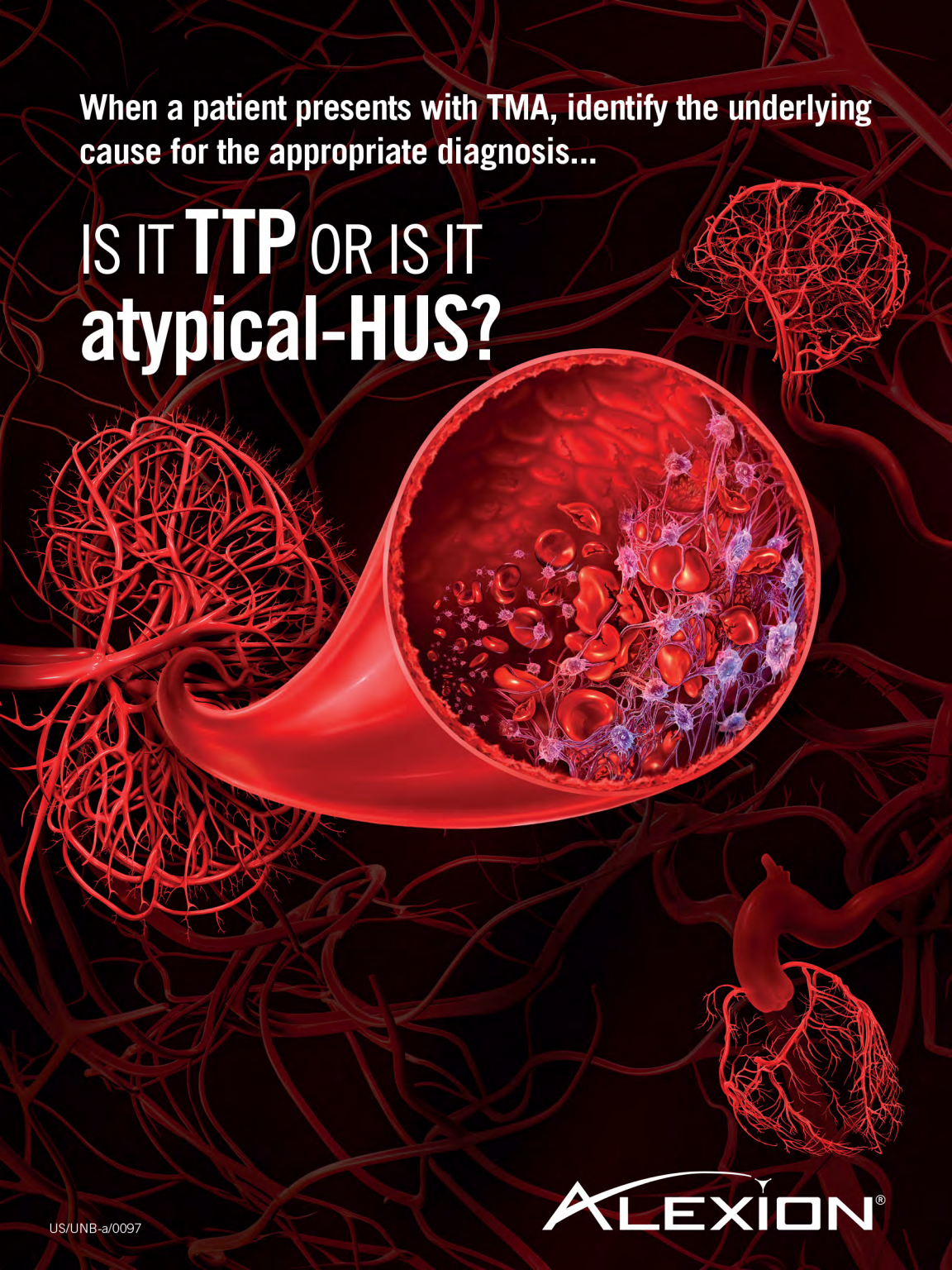
When a patient presents with TMA, identify the underlying cause for the appropriate diagnosis...

IS IT **TTP** OR IS IT **atypical-HUS?**



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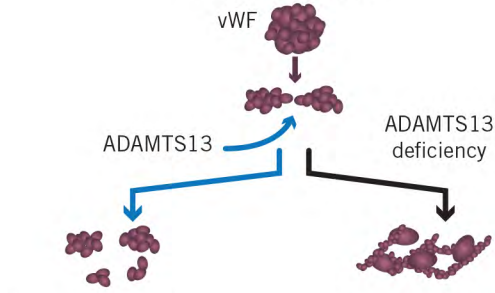
TTP and atypical-HUS are driven by different pathophysiologic processes and have different management goals[1-5]

TTP[1,2]

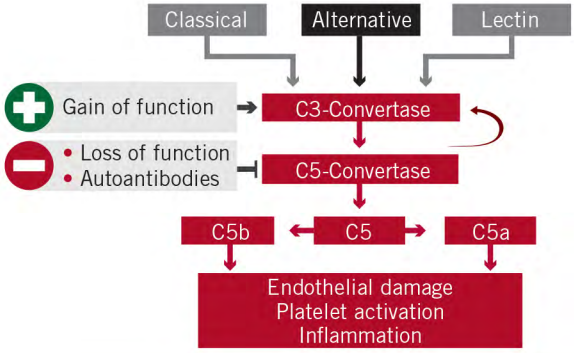
Insufficient ADAMTS13 activity (≤5%) leaves vWF intact



Suppress/remove inhibitor autoantibody; replace ADAMTS13[5]

Atypical-HUS[4,5]

Genetic defects lead to chronic uncontrolled activation of the complement system



Inhibit ongoing complement activation[5]

Identifying atypical-HUS as the underlying cause of TMA is critical to effective management decisions[2,6,7]

SCr level and platelet count can be used to predict ADAMTS13 activity with high probability in patients with TMA[8-13]

In a national registry of 214 patients with TMA, baseline SCr level and platelet count were identified as independently predictive values of ADAMTS13 deficiency[9,a]

Patient Characteristics	Adjusted Odds Ratio	95% CI	*P* Value
Creatinine level ≤200 µmol/L (2.3 mg/dL)	23.4	8.8-62.5	<0.001
Platelet count ≤30 x 10^9/L	9.1	3.4-24.2	<0.001

A patient with a TMA presenting with SCr level >1.7 to 2.3 mg/dL or platelet count >30 x 10^9/L is less likely to have severe ADAMTS13 deficiency (TTP) than those who meet neither criteria[9,b]

Multiple studies on a total of 806 patients with TMA have shown that baseline values of SCr and platelets at clinical presentation can rapidly and efficiently distinguish between sufficient and severely deficient ADAMTS13 activity[8-13]

SCr level and platelet count show statistical significance in predicting ADAMTS13 activity

	Association With Severe ADAMTS13 Deficiency: *P* Value	
Authors	Serum Creatinine Level	Platelet Count
Bentley, et al. 2010[8,c] (N=110)	0.0207	0.0034
Cataland, et al. 2012[12,b] (N=54)	<0.0001	<0.0001
Coppo, et al. 2010[9,a] (N=214)	<0.0001	<0.0001
Kremer Hovinga, et al. 2010[10,b] (N=261)	<0.001	<0.001
Shah, et al. 2013[13,d] (N=60)	0.0003	0.0001
George 2010[11,b] (N=107)	<0.001	<0.001

ADAMTS13 deficiency defined as ADAMTS13 activity: [a]<5% (mild deficiency=5%-20%), [b]<10%, [c]<15%, [d]<10%. ADAMTS13 assays generally have a sensitivity of 5%-10%.[1] Severely deficient ADAMTS13 activity is typically defined as <5%.[1,9]

PE/PI as treatment for atypical-HUS has been clinically harmful and/or ineffective[5,7,14,15]

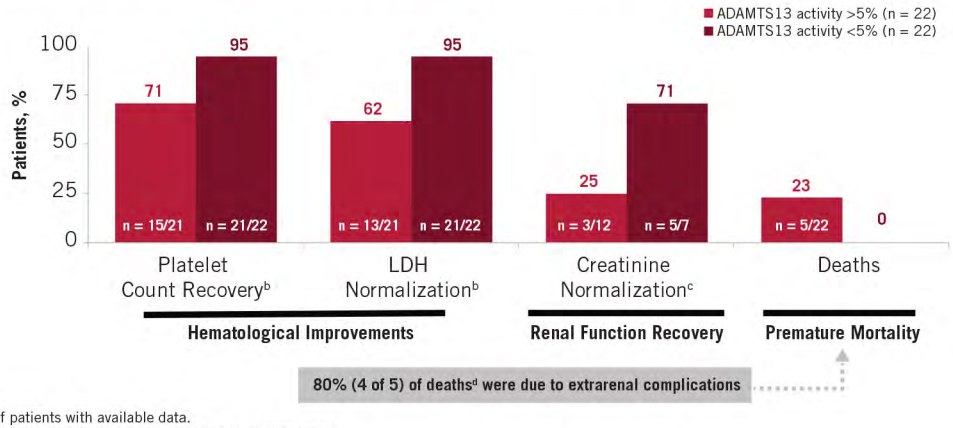
Complement dysregulation and TMA persist in patients with atypical-HUS on PE/PI, even if there is a transient impact on platelet count and LDH levels[16,17]

- PE/PI is not sufficient to remove mutant complement factors or replace deficient factors[16-19]
  - Apheresis procedures themselves may also lead to complement activation[20]
- Mean plasma levels of complement Ba,[a] a key marker of alternate complement pathway activity, are similarly elevated among patients with atypical-HUS receiving or not receiving PE or PI[17]

[a]Complement component Ba is formed upon activation of the alternative complement pathway and cleavage of factor B.[17]

Mortality outcomes differed in patients receiving PE with and without severe ADAMTS13 deficiency[21]

Rates of renal recovery and premature mortality in patients with severe or nonsevere ADAMTS13 activity undergoing PE/PI for the treatment of TMA (follow-up period up to 21 days)[21]



[b]Of patients with available data.
[c]Of patients with abnormal creatinine level at baseline.
[d]Non-ST-segment elevation MI/aspiration pneumonia, non-ST-segment elevation MI/abdominal abscess, multiorgan failure, respiratory failure, sepsis.

Patients receiving initial PE/PI have equally poor outcomes after 1 year compared with patients without initial PE/PI[22]

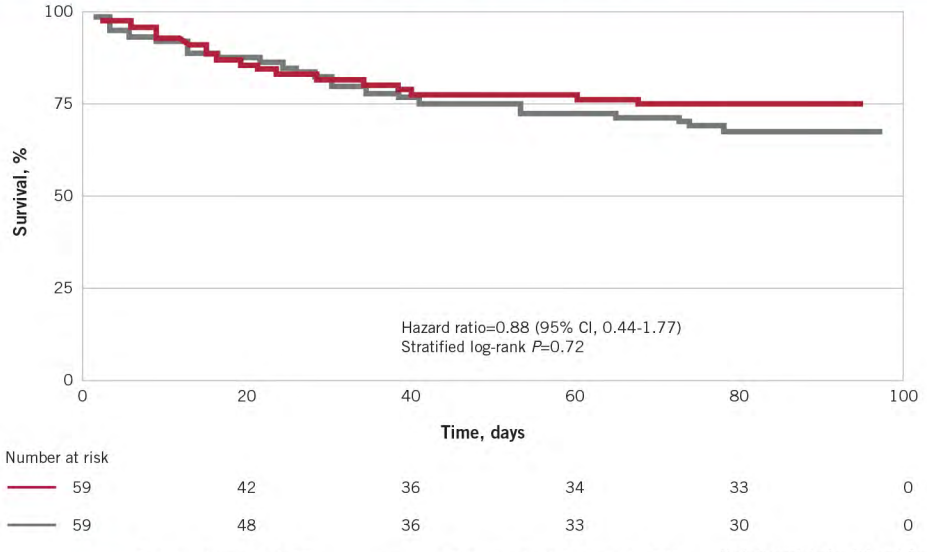
According to the American Society for Apheresis, PE in atypical-HUS receives *"Weak recommendation, low-quality or very low-quality evidence."*[23,e]

[e]This recommendation excludes atypical-HUS caused by MCP mutation.

atypical-HUS is a disease associated with chronic risk of complement-mediated TMA and life-threatening consequences[14,21,24]

Patients without severe ADAMTS13 deficiency do not have a significant clinical benefit from PE[25,a]

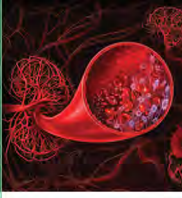
Kaplan-Meier survival analysis of patients without severe ADAMTS13 deficiency[25,b]



[a]Clinical benefit refers to impact on 90-day mortality, platelet count recovery, or hospital length of stay.[25] [b]Adult patients included in the Harvard TMA Research Collaborative registry (N=186, of whom 71 had received at least 1 TPE session) were matched based on clinical criteria, including age; sex; ethnicity; Charlson Comorbidity Index score; immunosuppression; history of prior solid organ or bone marrow transplant; presence of neurological symptoms, sepsis, shock, and/or multiorgan failure; platelet count; creatinine level; LDH level; and international normalized ratio.[25] [c]Mean number of TPE sessions: 5 (range, 3-7); mean units of plasma transfused: 58 (range, 38-83).[25]

Patients with atypical-HUS remain at risk of impaired renal function and death, regardless of any hematologic improvement after TPE/PI[21]

Patients with atypical-HUS diagnosis are at immediate and ongoing risk of progressive clinical deterioration despite intensive use of PE/PI[14,15]



Differential diagnosis for TMAs: atypical-HUS, TTP, and STEC-HUS

When a patient presents with TMA, identify the underlying cause for the appropriate diagnosis.[26-28]

Differential diagnosis for TMAs: atypical-HUS, TTP, and STEC-HUS[4,21,29,30]

Thrombocytopenia
Platelet count <150 × 10⁹/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	Renal impairment	GI symptoms
Confusion and/or **Seizures** and/or **Stroke** and/or **Other cerebral abnormalities**	**Elevated creatinine level** and/or **Decreased eGFR** and/or **Elevated blood pressure** and/or **Abnormal urinalysis results**	**Diarrhea ± blood** and/or **Nausea/vomiting** and/or **Abdominal pain** and/or **Gastroenteritis/pancreatitis**

Other Signs and Symptoms

CV symptoms	Pulmonary symptoms	Visual symptoms
MI and/or **Hypertension** and/or **Arterial stenosis** and/or **Peripheral gangrene**	**Dyspnea** and/or **Pulmonary hemorrhage** and/or **Pulmonary edema**	**Pain and blurred vision** and/or **Retinal vessel occlusion** and/or **Ocular hemorrhage**

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

While ADAMTS13 results are awaited, a platelet count >30 × 10⁹/L and/or SCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

≤5%[b] 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]Shiga-toxin/EHEC test is warranted in history/presence of GI symptoms.[4,21] [b]Range found in published data is <5%-10%.[4,21]

The information on this page is intended as educational information for health care providers. It does not replace a health care professional's judgment or clinical diagnosis.

Identifying atypical-HUS early as the underlying cause of TMA is critical to making appropriate management decisions.[2,4,6,7]

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif member 13; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EHEC, enterohemorrhagic *Escherichia coli*; GI, gastrointestinal; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; MI, myocardial infarction; PE, plasma exchange; PI, plasma infusion; SCr, serum creatinine; SLE, systemic lupus erythematosus; STEC, Shiga toxin-producing *E. coli*; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; vWF, von Willebrand factor.

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