

How do I recognize and diagnose atypical-HUS in the presence of autoimmune diseases?

- ▶ SLE/LN, SRC, and APS are known to cause TMA in patients¹
- ▶ The presence of persistent TMA despite management of the autoimmune disorders and a >10% ADAMTS13 activity* may suggest a diagnosis of atypical-HUS¹

In your patients with autoimmune diseases and persistent TMA, consider screening for atypical-HUS¹



**Have questions?
Contact your representative.**

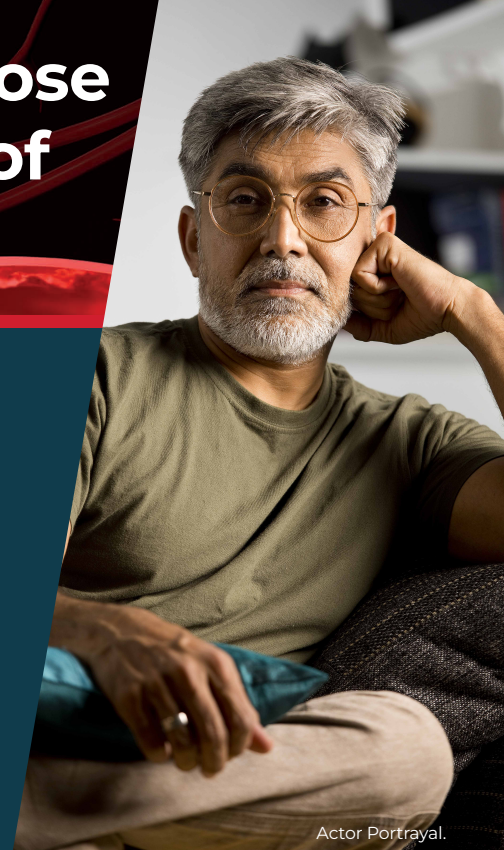


The information in this brochure is intended as educational information for healthcare professionals.
It does not replace a healthcare professional's judgment or clinical diagnosis.

^{*}Values in literature range from >5%-10%.¹

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13;
APS=antiphospholipid syndrome; HUS=hemolytic uremic syndrome; LN=lupus nephritis; SLE=systemic lupus erythematosus; SRC=scleroderma renal crisis; TMA=thrombotic microangiopathy.

ALEXION[®]
AstraZeneca Rare Disease



Actor Portrayal.

What is atypical-HUS?

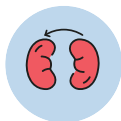
Thrombotic microangiopathy (TMA):

A serious medical syndrome characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and signs of organ involvement, including acute kidney injury.¹

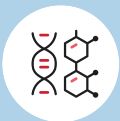
Atypical-hemolytic uremic syndrome (atypical-HUS):

A TMA caused by uncontrolled terminal complement activation—it requires urgent intervention to avoid poor clinical outcomes.¹

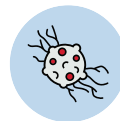
Complement-triggering conditions may lead to atypical-HUS in some patients^{1,2}



Kidney transplant^{1,2}



Autoimmune disorders¹



Cancer and cancer therapies^{1,2}



Drugs¹



Malignant hypertension³



Pregnancy/postpartum¹



Infection¹



Surgery or trauma¹



Glomerulonephritis¹

TMA in patients with SLE/LN may lead to serious consequences^{4,5}

SLE/LN

SLE



increased risk of in-hospital mortality in patients with SLE and TMA compared with patients with SLE without TMA, $P<0.001$ ^{4*}

LN



of LN patients with TMA (28/79) needed dialysis vs 5% of LN patients without TMA (4/79), $P<0.001$ ^{5†}



Screen for TMA in your patients with SLE/LN and rapidly determine the cause of TMA

⁴Based on a retrospective cohort study of 35,745 hospitalized patients with a primary discharge diagnosis of SLE from 2003 to 2014 from the US National Inpatient Sample database. Data are presented as an OR of in-hospital mortality of TMA SLE patients (12/188) vs non-TMA SLE patients (443/35,557; OR 5.54; $P<0.001$).⁴

⁵Based on a Chinese retrospective cohort of 79 patients with biopsy-proven LN-associated TMA and 79 without TMA, matched by gender, age, and LN classes from 2012 to 2021.⁵

LN=lupus nephritis; OR=odds ratio; SLE=systemic lupus erythematosus; TMA=thrombotic microangiopathy.

Which of your patients with SLE/LN should you screen for TMA?

SLE/LN



Patients with SLE/LN presenting with certain renal signs or symptoms despite management^{4,5*†}:

- ▶ New-onset AKI or malignant hypertension with or without signs of nephritis⁶
 - **AKI in SLE & TMA (43%)**
vs SLE only (15%), $P < 0.001^{4*}$
 - **AKI in LN & TMA (30%)**
vs LN only (14%), $P = 0.013^{5†}$



Patients presenting with new or worsening hematologic signs (thrombocytopenia and MAHA)^{1,2}

- ▶ Schistocytes finding on blood smear is indicative of MAHA due to TMA vs autoimmune hemolytic anemia⁷⁻¹⁰

Consider atypical-HUS in patients with SLE/LN who present with persistent TMA despite management of SLE/LN^{2,4,5}

*Based on a retrospective cohort study of 35,745 hospitalized patients with a primary discharge diagnosis of SLE from 2003 to 2014 from the US National Inpatient Sample database. Patients with SLE were categorized based on the presence of TMA during hospitalization⁴

†Based on a Chinese retrospective cohort of 79 patients with biopsy-proven LN-associated TMA and 79 without TMA, matched by gender, age, and LN classes from 2012 to 2021.⁵

AKI=acute kidney injury; HUS=hemolytic uremic syndrome; LN=lupus nephritis; MAHA=microangiopathic hemolytic anemia; SLE=systemic lupus erythematosus; TMA=thrombotic microangiopathy.

TMA in patients with SRC may lead to serious consequences¹¹⁻¹³

SRC

SRC



of patients with
SRC may present
**with evidence
of TMA^{11,12}**

Patients with SRC and
TMA can **progress to
ESKD or death^{12,13}**



**Screen for TMA in your patients with SRC
and rapidly determine the cause of TMA**

Which of your patients with SRC should you screen for TMA?

SRC



Patients with SRC and TMA are likely to:

- ▶ Present with **new or worsening** hematologic signs, including thrombocytopenia and MAHA^{14,15}



MAHA is found in approximately **50%** of **patients with SRC**¹⁵

Consider atypical-HUS in patients with SRC who present with persistent TMA despite management of SRC^{1,14,15}

TMA in patients with APS may lead to serious consequences^{16,17}

APS

APS



of patients with APS, in the ICU setting, are reported to present with TMA^{16*}



of patients with APS are reported to present with TMA^{17†}



of patients with APS and TMA (n=5) had a stroke compared with 33% of patients without TMA (n=61)^{17†}



Screen for TMA in your patients with APS and rapidly determine the cause of TMA

*French, national, multicenter, retrospective study conducted from January 2000 to September 2018, included all APS patients (134 patients with 152 episodes) admitted to 24 participating centers' ICUs with any new thrombotic (arterial, venous, or microvascular) manifestation.¹⁶

†Cross-sectional study including 66 primary APS patients, aged ≥18 years old, regularly followed at a private clinic.¹⁷

APS=antiphospholipid syndrome; ICU=intensive care unit; TMA=thrombotic microangiopathy.

Which of your patients with APS should you screen for TMA?

APS



Patients with APS presenting with renal involvement^{18,19}:

- ▶ **New or worsening** hypertension
- ▶ Proteinuria
- ▶ Decreased eGFR
- ▶ Acute kidney injury (AKI)

TMA is a characteristic histopathological finding of APS nephropathy (aPL-N)^{20,21}

Consider atypical-HUS if TMA persists after treating APS/CAPS

Differential diagnosis of atypical-HUS

Management needs differ for autoimmune-induced TMA and atypical-HUS; rapid differentiation is crucial¹

STEP 1

STEP 2

STEP 3

Recognize TMA as early as possible via labs or kidney biopsy¹

Thrombocytopenia

1

- ▶ Platelets $<150 \times 10^9/L$ or
▶ **>25% decrease from baseline**

CLINICAL TRIAD

Microangiopathic hemolytic anemia

2

- ▶ Elevated LDH, decreased hemoglobin, decreased haptoglobin, and/or schistocytes
- ▶ *Schistocytes may not appear on initial evaluation; daily review of blood smears is advised*

One or more signs and symptoms of organ damage*

3



Neurological symptoms

- ▶ Confusion, stroke, seizures, and/or other cerebral abnormalities



Kidney function impairment

- ▶ Elevated creatinine levels, decreased eGFR, elevated blood pressure, and/or abnormal urinalysis



Cardiovascular symptoms

- ▶ MI, hypertension, arterial stenosis, and/or peripheral gangrene



GI symptoms

- ▶ Diarrhea $\pm$ blood, nausea/vomiting, abdominal pain, and/or gastroenteritis/pancreatitis



Pulmonary symptoms

- ▶ Dyspnea, pulmonary hemorrhage, and/or pulmonary edema



Visual symptoms

- ▶ Pain, blurred vision, retinal vessel occlusion, and/or ocular hemorrhage

*This is not a complete list of the signs and symptoms of atypical-HUS, and not all signs and symptoms may be present simultaneously.

eGFR=estimated glomerular filtration rate; GI=gastrointestinal; HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; MI=myocardial infarction; TMA=thrombotic microangiopathy.

Differential diagnosis of atypical-HUS

Management needs differ for autoimmune-induced TMA and atypical-HUS; rapid differentiation is crucial¹

STEP 1	STEP 2	STEP 3
Rapidly conduct appropriate testing		
A Draw blood before initiating PE/PI and order an ADAMTS13 test immediately¹ While waiting for ADAMTS13 results ▶ A platelet count >30,000 mm³ and/or SCr level >1.7-2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)¹ ▶ A PLASMIC score of ≤5 should trigger suspicion of atypical-HUS²²	B Perform testing to determine if autoimmune disease or other triggers may be the cause of TMA ▶ SLE^{23,24} ▶ Antinuclear antibodies (ANA) ▶ aPL: anti-cardiolipin antibodies or anti-β2GPI antibodies or lupus anticoagulant assay (LAC) ▶ Anti-dsDNA antibodies or anti-Smith antibodies ▶ Anti-Clq ▶ SRC²⁵ ▶ Anti-centromere antibody or centromere pattern on ANA ▶ Anti-Scl70 or anti-RNA polymerase III ▶ APS²⁶ ▶ aPL by coagulation-based assay: LAC assay ▶ aPL by solid phase assay: anti-cardiolipin antibodies and anti-β2GPI antibodies ▶ Shiga toxin/EHEC test to rule out STEC-HUS*	C Other tests^{1,27} ▶ Blood smear to test for the presence of schistocytes (may require repeat testing) ▶ Kidney biopsy (can help identify TMA) ▶ Complement level testing[†]

*Shiga toxin/EHEC test is warranted with a history/presence of GI symptoms.¹

†Complement testing is not definitive.²

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aPL=antiphospholipid antibody; APS=antiphospholipid syndrome; β2GPI=β2-glycoprotein 1; Clq=complement component 1q; DNA=deoxyribonucleic acid; ds=double stranded; EHEC=enterohemorrhagic *Escherichia coli*; GI=gastrointestinal; HUS=hemolytic uremic syndrome; PE=plasma exchange; PI=plasma infusion; PLASMIC=Platelet count, Lysis (hemolysis), Active cancer (absence of), Stem cell or solid organ transplant history (absence of), Mean corpuscular volume, International normalized ratio, and Creatinine; RNA=ribonucleic acid; SCr=serum creatinine; SLE=systemic lupus erythematosus; SRC=scleroderma renal crisis; STEC-HUS=Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

Differential diagnosis of atypical-HUS

Management needs differ for autoimmune-induced TMA and atypical-HUS; rapid differentiation is crucial¹

STEP 1	STEP 2	STEP 3	
Determine the cause of TMA			
TMA resolves after management of autoimmune disease ► Autoimmune-induced TMA^{1,28} (eg, SLE/LN, APS/CAPS, SRC)	 >10% ADAMTS13 activity^{1*} ► Strongly consider atypical-HUS	≤10% ADAMTS13 activity^{1†} ► TTP	Shiga toxin/ EHEC positive¹ ► STEC-HUS
 ► Persistent TMA despite addressing the primary cause (eg, autoimmune disease) may indicate atypical-HUS¹ ► Atypical-HUS is a medical emergency; <u>once diagnosed, treatment should not be delayed while other tests are carried out</u>¹			

*Values in literature range from >5%-10%.¹

†Values in literature range from <5%-10%.¹

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APS=antiphospholipid syndrome; CAPS=catastrophic antiphospholipid syndrome; EHEC=enterohemorrhagic *Escherichia coli*; HUS=hemolytic uremic syndrome; LN=lupus nephritis; SLE=systemic lupus erythematosus; SRC=scleroderma renal crisis; STEC-HUS=Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

Consider and evaluate for atypical-HUS in your patients with autoimmune diseases and persistent TMA despite management

Business card holder

ONESOURCE[®]
Personalized Patient Support from Alexion

Complimentary, personalized patient support program

We can help with:



Providing educational materials about atypical-HUS along the patient journey



Connecting patients for peer-to-peer discussions through Peer Connects



Sharing information about live and virtual community events, advocacy groups, and other resources



Offering support for patients and their healthcare providers in navigating insurance coverage and access

HUS=hemolytic uremic syndrome; TMA=thrombotic microangiopathy.

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