Identifying atypical-HUS and renal-limited TMA with kidney biopsy

- Atypical-HUS is a TMA caused by complement dysregulation—it requires urgent intervention to avoid poor clinical outcomes[1]
- Patients with atypical-HUS might not present with complete hematologic signs, leading to a potential missed diagnosis[2-4]

Communicate findings of TMA on kidney biopsy and potential causes of TMA, including atypical-HUS, to the ordering healthcare provider

Have questions?
Contact your representative.

aHUS Source

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.

HUS=hemolytic uremic syndrome; TMA=thrombotic microangiopathy.

ALEXION®
AstraZeneca Rare Disease

What are TMA and atypical-HUS, and how are they related?

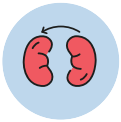
Thrombotic microangiopathy (TMA):

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

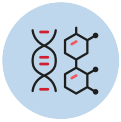
Atypical-hemolytic uremic syndrome (atypical-HUS):

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[1,5]



Kidney transplant[1,5]



Autoimmune disorders[1]

Cancer and cancer therapies[1,5]

Drugs[1]

Malignant hypertension[6]

Pregnancy/ postpartum[1]

Infection[1]

Surgery or trauma[1]

Glomerulonephritis[1]

This is not an all-inclusive list of atypical-HUS triggers.

What is a renal-limited TMA?

Renal-limited TMA is defined as **TMA without signs of thrombocytopenia and/or microangiopathic hemolytic anemia (MAHA)** which can be identified with a kidney biopsy.[4]

TMA with systemic hematologic signs (classic triad)[1,4]

Thrombocytopenia

- Platelets <150 × 10^9/L or >25% decrease from baseline

AND

MAHA

- Elevated LDH, decreased hemoglobin, decreased haptoglobin, and/or schistocytes

AND

One or more signs and symptoms of organ damage

- Kidney function impairment, neurological symptoms, pulmonary symptoms, GI symptoms, cardiovascular symptoms, and visual symptoms

Renal-limited TMA[4]

Absence of the classic triad of TMA with renal impairment

- Could have varying features of thrombocytopenia and MAHA but not meet the classic triad of TMA
- Varying definitions of renal-limited TMA in the literature[3,4]

KEY TAKEAWAY 1:
TMA can be present in a patient and not fit the classic triad definition of a TMA.

KEY TAKEAWAY 2:
Kidney biopsy can be used to identify patients with renal-limited TMA.

GI=gastrointestinal; LDH=lactate dehydrogenase; TMA=thrombotic microangiopathy.

Assessment of clinical characteristics and biological parameters in kidney biopsy–proven TMA: French MATRIX cohort

	Study 1: Halimi JM, et al. 2025[3,7]	**Study 2:** Maisons V, et al. 2024[2]
Who was studied?	Observational, longitudinal study of patients aged ≥18 years with biopsy of a native kidney admitted from Jan 1, 2009, to Dec 31, 2023, across 25 nephrology departments in France.	Observational, longitudinal study of patients aged ≥18 years with biopsy of a native kidney admitted from Jan 1, 2009, to Dec 31, 2022, across 20 nephrology departments in France.
What was done?	Kidney biopsies were performed because of acute kidney injury and/or proteinuria, in the absence of hematologic evidence of TMA.	Kidney biopsies were performed because of acute kidney injury with or without evidence of hematologic TMA.
How were study parameters defined?	**TMA** causes were classified per the 2017 KDIGO classification. **Native kidney biopsies were analyzed, and TMA was diagnosed** by the local renal pathologist according to the usual criteria. **Atypical-HUS** was defined as TMA without KDIGO-listed cause per 2017 KDIGO classification. In patients diagnosed with atypical-HUS, a subset was defined as **complement-mediated atypical-HUS** (ie, with dysregulation of CAP because of the presence of antibodies or pathogenic variants).	**TMA** causes were classified per the 2017 KDIGO classification. **Renal-limited TMA** was defined by the local renal pathologist according to the usual criteria, and **TMA with hematologic features** was defined by the physician of each center using classic parameters.* **Atypical-HUS** was defined as TMA without KDIGO-listed cause per 2017 KDIGO classification. In patients diagnosed with atypical-HUS, a subset was defined as **complement-mediated atypical-HUS** (ie, with dysregulation of CAP because of the presence of antibodies or pathogenic variants or isolated low C3).
What were the study limitations?	Analysis of kidney biopsies and diagnosis of renal-limited TMA were subject to local pathologist interpretation. Only a small number of patients were evaluated for complement-mediated atypical-HUS. Results are not applicable to all patients with TMA, as not all have renal involvement or require a kidney biopsy, especially when considering the risk of bleeding in those with thrombocytopenia.	Only a small number of patients were evaluated for complement-mediated atypical-HUS. Results are not applicable to all patients with TMA, as not all have renal involvement or require a kidney biopsy, especially when considering the risk of bleeding in those with thrombocytopenia.

*Low platelet count, low hemoglobin level, high LDH level, schistocytosis, and low haptoglobin level.[3]

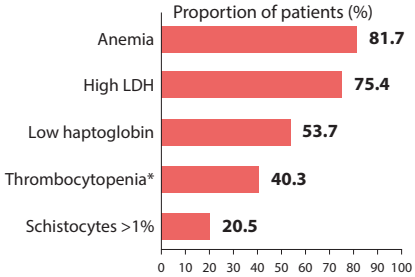
C3=complement component 3; CAP=complement alternative pathway; HUS=hemolytic uremic syndrome; KDIGO=Kidney Disease: Improving Global Outcomes; LDH=lactate dehydrogenase; TMA=thrombotic microangiopathy.

Patients with renal-limited TMA might not present with complete hematologic signs, leading to a potential missed diagnosis[3]

Study 1: Halimi JM, et al. 2025

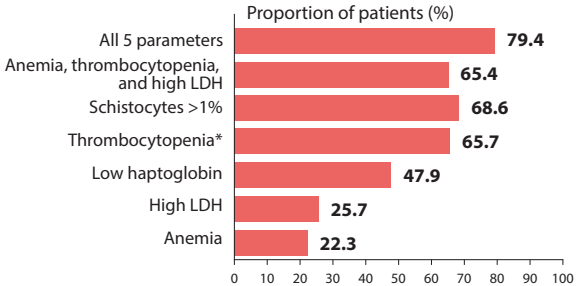
This may not be reflective of the greater TMA population, given that not all TMA patients require a kidney biopsy.

Presence of hematologic signs at the time of TMA diagnosis (n=967):

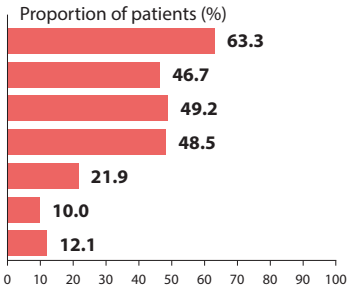


Rate of missed diagnosis in patients when using a single or combined hematologic signs:

Atypical-HUS (n=402/967)



Complement-mediated atypical-HUS (n=66/402)†



Limitations of the study included that analysis of kidney biopsies and diagnosis of renal-limited TMA were subject to local pathologist interpretation, and only a small number of patients were evaluated for complement-mediated atypical-HUS. Results are not applicable to all patients with TMA, as not all have renal involvement or require a kidney biopsy, especially when considering the risk of bleeding in those with thrombocytopenia.

*Does not include those with a >25% decrease from baseline, as only one laboratory value was analyzed.

†Data also referred to here as C-mediated TMA.

HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; TMA=thrombotic microangiopathy.

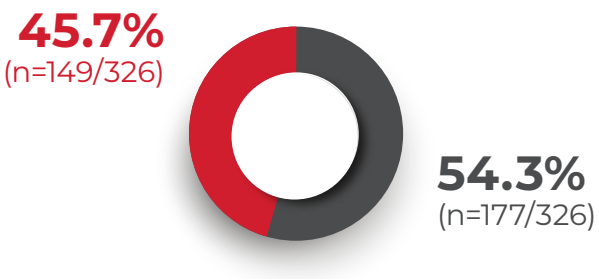
Scan the QR code and access the full publication for more information on methods and results.

Atypical-HUS patients can present with renal-limited TMA[2]

Study 2: Maisons V, et al. 2024

This may not be reflective of the greater TMA population, given that not all TMA patients require a kidney biopsy.

~43% (n=326/757)
of patients with kidney biopsy–proven TMA had atypical-HUS



~21% (n=69/326)
of patients with atypical-HUS had complement-mediated atypical-HUS

Renal-limited TMA Systemic (hematologic) TMA

Limitations of the study included that only a small number of patients were evaluated for complement-mediated atypical-HUS and results are not applicable to all patients with TMA, as not all have renal involvement or require a kidney biopsy, especially when considering the risk of bleeding in those with thrombocytopenia.

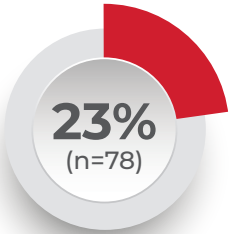
HUS=hemolytic uremic syndrome; TMA=thrombotic microangiopathy.

Scan the QR code and access the full publication for more information on methods and results.

Patients with renal-limited TMA can still experience poor outcomes[2]

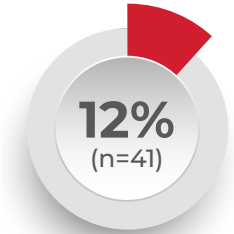
Study 2: Maisons V, et al. 2024

This may not be reflective of the greater TMA population, given that not all TMA patients require a kidney biopsy.



Kidney replacement therapy during hospitalization/ follow-up

Major cardiovascular event during hospitalization



Death during hospitalization/ follow-up

TMA=thrombotic microangiopathy.

Evaluate kidney biopsy for findings of active and chronic lesions of TMA

	Active lesions[8]	Chronic lesions[8]
Glomeruli 	▸ Thrombi ▸ Endothelial swelling or denudation ▸ Fragmented red blood cells ▸ Subendothelial flocculent material by EM ▸ Mesangiolysis ▸ Microaneurysms	▸ Double contours of peripheral capillary walls by LM with variable mesangial interposition ▸ New subendothelial basement membrane by EM ▸ Widening of the subendothelial zone by EM
Arterioles 	▸ Thrombi ▸ Endothelial swelling or denudation ▸ Intramural fibrin ▸ Fragmented red blood cells ▸ Intimal swelling ▸ Myocyte necrosis	▸ Hyaline deposits
Arteries 	▸ Thrombi ▸ Myxoid intimal swelling ▸ Intramural fibrin ▸ Fragmented red blood cells	▸ Fibrous intimal thickening with concentric lamination (onion skin)

A biopsy can show features of both active and chronic lesions[9]

Morphological features do not allow identification of etiology[8]

Discuss findings and differential diagnosis with ordering physicians to determine the underlying cause of TMA[8]

8 EM=electron microscopy; LM=light microscopy; TMA=thrombotic microangiopathy.

Communicate biopsy findings of TMA and potential causes of TMA, including atypical-HUS

Biopsy findings of TMA

Histologic insights

- Active, chronic, or mixed[1]
- Biopsy alone cannot differentiate the cause of TMA[1]:
  - **Atypical-HUS**, TTP, and other causes of TMA (autoimmune disease, malignant hypertension, kidney transplant, cancer, drug-induced [eg, cancer therapy, immunosuppressive, and other drugs], pregnancy, infection, surgery, and glomerulonephritis)[1]
- Prognostic information[10]

Additional clinical action: determine the cause of TMA[1]

- **Order ADAMTS13**
- Order a Shiga toxin/EHEC test to rule out STEC-HUS*
- Rule out other causes of TMA
- **Persistent TMA** despite management or unidentified secondary cause may indicate atypical-HUS
- Complement testing†; atypical-HUS genetic panel

Dialogue with clinician[1]

- **Narrow differential diagnosis to possible causes of TMA, including atypical-HUS**
- Leverage additional lab tests as appropriate to help determine cause of TMA
- Review clinical and family history for additional insights
- When appropriate, implications for renal transplantation

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

†Complement testing is not definitive.[1]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; EHEC=enterohemorrhagic *Escherichia coli;* HUS=hemolytic uremic syndrome; STEC-HUS=Shiga toxin–producing *Escherichia coli* hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

Rapidly order and conduct appropriate testing in patients with TMA

STEP 1 | **STEP 2**

Rapidly conduct appropriate testing

A — Draw blood before initiating PE/PI and order an ADAMTS13 test immediately[1]

While waiting for ADAMTS13 results

- A platelet count >30,000 mm^3 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-HUS[11]

B — Order appropriate testing to rule out other causes of TMA[1]

- Eg, autoimmune disease, malignant hypertension, kidney transplant, cancer, drug-induced, pregnancy, infection, surgery, and glomerulonephritis
- Shiga toxin/EHEC test to rule out STEC-HUS*

C — Other tests[1] (if medically appropriate)

- Blood smear to test for the presence of schistocytes (may require repeat testing)
- Complement level testing†
- Complement genetic testing†
- Complement functional assays

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

†Complement level and genetic testing are not definitive for an atypical-HUS diagnosis.[1]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; 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; SCr=serum creatinine; STEC-HUS=Shiga toxin–producing *Escherichia coli* hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

Determine if atypical-HUS is the cause of TMA in your patients according to ADAMTS13 results and clinical history

STEP 1

STEP 2

Determine the cause of TMA

Trigger-induced TMA (eg, autoimmune, kidney transplant, malignant hypertension, drug-induced, pregnancy, infection, surgery, etc)[1]

- TMA resolves after addressing the primary cause

>10% ADAMTS13 activity[1]*

- **Strongly consider atypical-HUS**

≤10% ADAMTS13 activity[1]†

- TTP

Shiga toxin/ EHEC positive[1]

- STEC-HUS

- **Persistent TMA despite addressing the primary cause may indicate atypical-HUS[1]**
- **Atypical-HUS is a medical emergency; once diagnosed, treatment should not be delayed while other tests are carried out[1]**
- **Management needs differ for atypical-HUS compared to other causes of TMA; rapid differentiation is crucial[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; EHEC=enterohemorrhagic *Escherichia coli;* HUS=hemolytic uremic syndrome; STEC-HUS=Shiga toxin–producing *Escherichia coli* hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

Consider and evaluate atypical-HUS in your patients with TMA found on kidney biopsy

- Be aware that patients with atypical-HUS might not present with complete hematologic signs, leading to a potential missed diagnosis[3]

Communicate findings of TMA on kidney biopsy and potential causes of TMA, including atypical-HUS, to the ordering healthcare provider.

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

Business card guide

HUS=hemolytic uremic syndrome; TMA=thrombotic microangiopathy.

References: 1. Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14 Suppl 11(11):2-15. **2.** Maisons V, et al. *Kidney Int.* 2024;105(5):1100-1112. **3.** Halimi JM, et al. *Kidney Int Rep.* 2025;10(6):1950-1959. **4.** van Doorn DPC, et al. *Mod Pathol.* 2025;38(4):100690. **5.** Azoulay E, et al. *Chest.* 2017;152(2):424-434. **6.** Asif A, et al. *J Nephrol.* 2017;30(3):347-362. **7.** Halimi JM, et al. *Kidney Int Rep.* 2025;10(6):1950-1959. [supplementary]. **8.** Goodship TH, et al. *Kidney Int.* 2017;91(3):539-551. **9.** Kovala M, et al. *J Clin Med.* 2022;11(11):3124. **10.** Laszik ZG, et al. Thrombotic Microangiopathies. Abdominal Key. June 21, 2016. Accessed March 31, 2026. https://abdominalkey.com/thrombotic-microangiopathies-2/#F16-18 **11.** Uriol-Rivera MG, et al. *BMC Nephrol.* 2025;26(1):241.

ALEXION®
AstraZeneca Rare Disease