

Identifying and diagnosing atypical-HUS in the presence of drugs

- ▶ Certain drugs have been associated with TMA^{1,2}

Consider atypical-HUS in patients who present with persistent TMA despite stopping the offending agent for an adequate amount of time³



**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.

HUS=hemolytic uremic syndrome; TMA=thrombotic microangiopathy.



ALEXION[®]
AstraZeneca Rare Disease

Certain drugs have been associated with TMA¹



**Rising drug-related TMA
FDA adverse event reports:
From 2004 (n=241)
to 2024 (n=1306)⁴**

The number of drugs associated with drug-induced TMA is increasing¹

- ▶ Some drugs are frequently used in clinical settings, eg, as antibiotics or antiplatelet therapy¹
- ▶ The heterogeneity of these agents requires physicians from several different areas to be familiar with drug-induced TMA¹

**Some drug-induced TMAs may be associated
with complement activation^{1,2*}**

Mechanisms of action

Dose- or duration-related toxic reactions:

- ▶ Direct endothelial injury from cumulative drug exposure¹
- ▶ Different mechanisms of action including prothrombotic activation, inhibition of VEGF pathway, or dysregulation of transcription factors leading to endothelial injury¹

Immune-mediated reactions:

- ▶ Hypersensitivity to a given drug¹
- ▶ Production of reactive antibodies that interact with platelets, endothelium, and circulating factors¹
- ▶ Leads to platelet-thrombi formation and endothelial damage; predisposes to TMA development¹

**Some drugs can cause TMA both directly and
through immune effects¹**

^{*}Based on a literature review of published drug-induced TMA case reports/series; retrospective data, not a controlled or prospective study. For patients with drug-induced TMA who had a renal biopsy, 38/66 showed the presence of complement factors on immunofluorescence staining. Among the 25 patients who had a concomitant complement activation, 9/25 also had decreased serum complement levels (mainly characterized by isolated C3 reduction).¹

C3=complement component 3; FDA=Food and Drug Administration; TMA=thrombotic microangiopathy; VEGF=vascular endothelial growth factor.

How do patients with drug-induced TMA present?

Dose or duration-related toxicity⁵ (Type I pattern)

Onset

- ▶ No clear time of onset after exposure¹

Phenotype

- ▶ Can often manifest as progressive kidney failure^{5,6}
- ▶ Often with hypertension⁵
- ▶ Kidney injury may be irreversible^{5,6}

Notes

- ▶ Different mechanisms of action^{1,5}

Immune-mediated reactions^{1,5} (Type II pattern)

Onset

- ▶ Acute onset of symptoms, including early or after prolonged exposure⁵⁻⁷

Phenotype

- ▶ Severe systemic symptoms, often with anuric acute kidney injury⁵
- ▶ Chronic kidney disease with hypertension may occur⁵

Immunosuppressive drugs can cause TMA

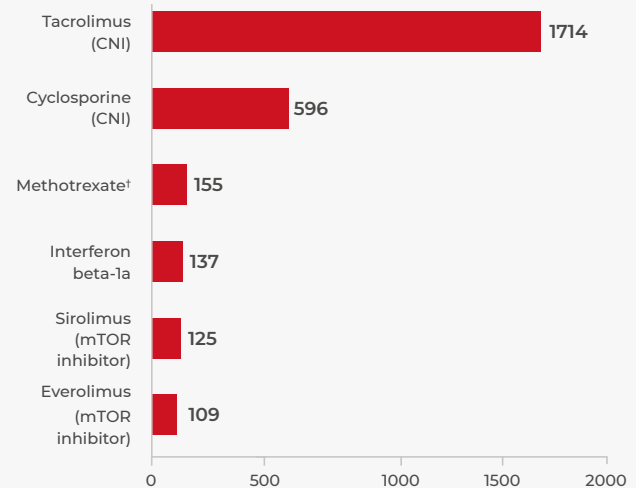
Immunosuppressive drugs with the highest number of reported TMAs^{4*}

Calcineurin inhibitors (CNIs)^{8,9}

- Use is associated with endothelial dysfunction, leading to intravascular platelet aggregation⁹

mTOR inhibitors (eg, Everolimus)¹

- Interfere with endothelial cells and with autophagy (a system of intracellular degradation maintaining cell homeostasis)¹



⁴Based on a study of FDA adverse event reporting from 2004 to 2024.⁴

[†]The respective package inserts do not include risk of TMA.⁴

FDA=Food and Drug Administration; mTOR=mechanistic target of rapamycin;
TMA=thrombotic microangiopathy.

Adapted from Yin Y, et al. 2025⁴

Certain cancer therapies known to cause TMA¹

Chemotherapies and targeted cancer drugs represent frequently reported triggers for drug-induced TMA and include¹:

Cytotoxic therapies (eg, gemcitabine)

- ▶ Can cause TMA in cancer patients^{1,8}

VEGF inhibitors (eg, bevacizumab)

- ▶ Intravitreal administration of VEGF inhibitors for age-related macular degeneration and diabetic retinopathy has been associated with cases of TMA^{1,10}
- ▶ Interrupt the survival signaling, which results in endothelial injury and TMA⁸

Proteasome inhibitors (eg, carfilzomib)

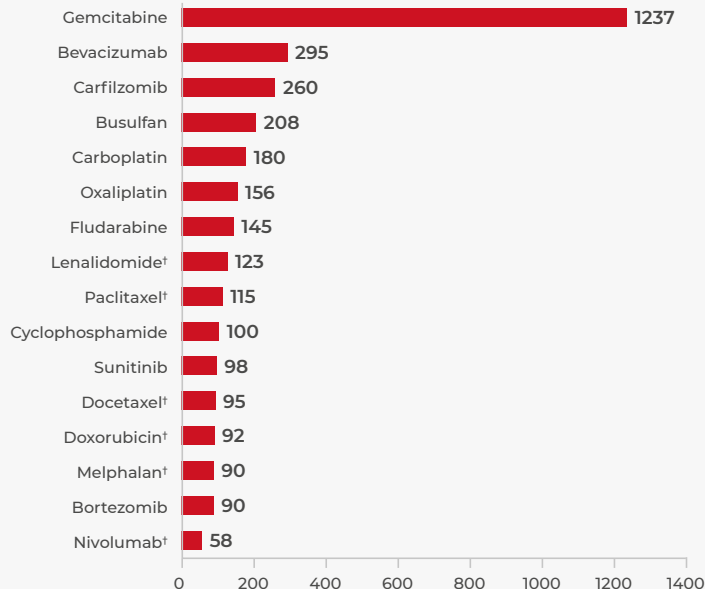
- ▶ Carfilzomib-induced TMA has been reported in patients with multiple myeloma^{8,11}

^{*}Based on a study of FDA adverse event reporting from 2004 to 2024.⁴

[†]The respective package inserts do not include risk of TMA.⁴

FDA=Food and Drug Administration; TMA=thrombotic microangiopathy; VEGF=vascular endothelial growth factor.

Chemotherapies and targeted cancer drugs with the highest number of reported TMAs^{4*}

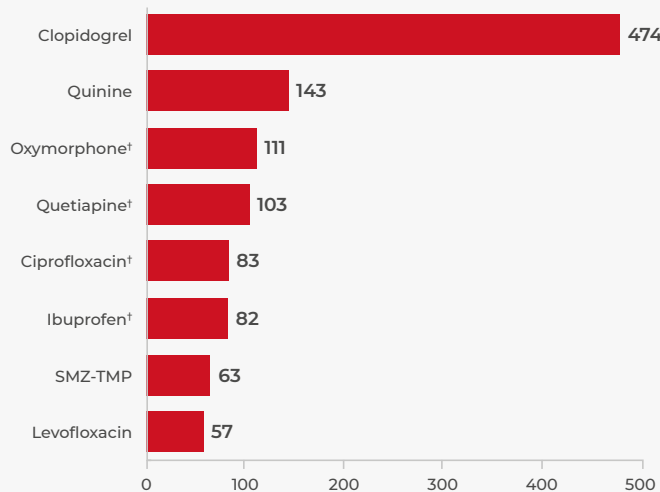


Adapted from Yin Y, et al. 2025⁴

Other drugs

The number of drugs that may be associated with drug-induced TMA is increasing¹

Other drugs with the highest number of reported TMAs^{4*}



Adapted from Yin Y, et al. 2025⁴

Additional drugs reported to be associated with TMA^{1,4}

- ▶ Foscarnet^{4†}
- ▶ Onasemnogene abeparvovec¹
- ▶ Atovaquone^{4†}
- ▶ Micafungin^{4†}
- ▶ Ketoprofen^{4†}
- ▶ Cocaine¹

*Based on a study of FDA adverse event reporting from 2004 to 2024.⁴

†The respective package inserts do not include risk of TMA.⁴

FDA=Food and Drug Administration; SMZ-TMP=sulfamethoxazole-trimethoprim; TMA=thrombotic microangiopathy.

How do you recognize drug-induced TMA in your patients?

Kidney-predominant pattern (*most common end-organ damage in TMA*)



- ▶ **New or worsening** hypertension and decrease in eGFR^{3,5}
- ▶ Progressive or persistent kidney dysfunction despite hematologic recovery⁵

Unexplained extra-renal manifestations (eg, neurologic)



- ▶ Confusion, headache, visual changes, myocardial infarction, or gastrointestinal pain³

Hematologic manifestations



- ▶ Thrombocytopenia and microangiopathic hemolytic anemia (eg, schistocytes on smear); ADAMTS13 activity of $>10\%$ ^{3,12}
- ▶ Distinguish from myelosuppression¹²

Other clinical clues



- ▶ Medications commonly associated with TMA^{1,5,12}

What is atypical-HUS?

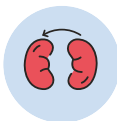
Thrombotic microangiopathy (TMA):

A serious medical syndrome characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and signs of organ involvement, including acute kidney injury.³

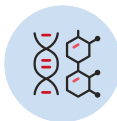
Atypical-hemolytic uremic syndrome (atypical-HUS):

A TMA caused by uncontrolled terminal complement activation—it requires urgent intervention to avoid poor clinical outcomes.³

Complement-triggering conditions may lead to atypical-HUS in some patients^{3,13}



Kidney transplant^{3,13}



Autoimmune disorders³



Cancer and cancer therapies^{3,13}



Drugs³



Malignant hypertension¹⁴



Pregnancy/postpartum³



Infection^{3,13}



Surgery or trauma³



Glomerulonephritis³

Differential diagnosis of atypical-HUS

Management needs differ for drug-induced TMA and atypical-HUS; rapid differentiation is crucial^{1,3}

STEP 1

STEP 2

STEP 3

Recognize TMA as early as possible³

Thrombocytopenia

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

1

CLINICAL
TRIAD

Microangiopathic hemolytic anemia

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

2

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

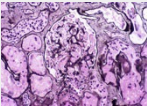
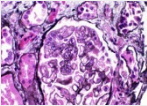
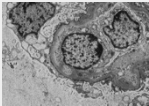
- ▶ Pain, blurred vision, retinal vessel occlusion, and/or ocular hemorrhage

*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 drug-induced TMA and atypical-HUS; rapid differentiation is crucial¹³

STEP 1	STEP 2	STEP 3
Order additional tests		
A Draw blood before initiating PE/PI and order an ADAMTS13 test immediately³ (and with quick turnaround time, when possible) While waiting for ADAMTS13 results ▶ A platelet count $>30,000 \text{ mm}^3$ and/or SCr level $>1.7\text{-}2.3 \text{ mg/dL}$ almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)³ ▶ The PLASMIC score is a validated tool for predicting ADAMTS13 activity^{15,16} – A PLASMIC score of ≤ 5 should trigger suspicion of atypical-HUS¹⁷	B Additional tests³ ▶ Rule out secondary causes of TMAs ▶ Blood smear to test for the presence of schistocytes (may require repeat testing) ▶ Shiga toxin/EHEC test to rule out STEC-HUS* Additional considerations¹ ▶ Withdraw the suspected causative drug ▶ Provide supportive care	C Optional tests^{3,18} (if medically appropriate) 1. Kidney biopsy 2. Complement level testing[†] Examples of kidney biopsy findings¹⁸    TMA with fibrin thrombi within glomerular capillary loops TMA in the chronic stage with basement membrane splitting TMA in the chronic stage with new basement membrane formation Figures reproduced from Lusco MA, et al. 2016¹⁸

*Shiga toxin/EHEC test is warranted with a history/presence of GI symptoms.³

[†]Complement testing is not definitive.³

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.

Differential diagnosis of atypical-HUS

Management needs differ for drug-induced TMA and atypical-HUS; rapid differentiation is crucial^{1,3}

STEP 1	STEP 2		STEP 3
Determine the cause of TMA			
TMA resolves after adequate time after discontinuing offending agent¹ ► Drug-induced TMA	 >10% ADAMTS13 activity^{3*} ► Strongly consider atypical-HUS	≤10% ADAMTS13 activity^{3†} ► TTP	Shiga toxin/ EHEC positive³ ► STEC-HUS
 ► Persistent TMA despite addressing the primary cause (eg, discontinuing the suspected offending agent) may indicate atypical-HUS³ ► Atypical-HUS is a medical emergency; once diagnosed, <u>treatment should not be delayed while other tests are carried out</u>³			

*Values in literature range from >5%-10%.³

†Values in literature range from <5%-10%.³

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 atypical-HUS in patients who present with persistent TMA despite addressing the primary cause (eg, discontinuing the suspected offending agent)³

Business card holder

HUS=hemolytic uremic syndrome; TMA=thrombotic microangiopathy.

References: **1.** Mazziarli T, et al. *Front Pharmacol.* 2023;13:1088031. **2.** Camilleri M, et al. *Br J Haematol.* 2021;193(4):750-760. **3.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(11) (suppl 11):2-15. **4.** Yin Y, et al. *Front Pharmacol.* 2025;16:1658963. **5.** George JN, Nester CM. *N Engl J Med.* 2014;371(7):654-666. **6.** Al-Nouri ZL, et al. *Blood.* 2015;125(4):616-618. **7.** Izzedine H, et al. *Am J Kidney Dis.* 2015;66(5):857-868. **8.** Hanna RM, et al. *Adv Chronic Kidney Dis.* 2022;29(2):149-160.e1. **9.** Niinomi I, et al. *Int J Clin Pharmacol Ther.* 2020;58:543-549. **10.** Hanna RM, et al. *Front Med (Lausanne).* 2020;7:579603. **11.** Gavrilaki E, et al. *J Clin Med.* 2022;11(12):3355. **12.** Aklilu AM, Shirali AC. *Kidney360.* 2023;4(3):409-422. **13.** Azoulay E, et al. *Chest.* 2017;152(2):424-434. **14.** Asif A, et al. *J Nephrol.* 2017;30(3): 347-362. **15.** Wynick C, et al. *Thromb Res.* 2020;196:335-339. **16.** Tufano A, et al. *Blood Transfus.* 2023;21(4):345-349. **17.** Uriol-Rivera MG, et al. *BMC Nephrol.* 2025;26(1):241. **18.** Lusco MA, et al. *Am J Kidney Dis.* 2016;67(6):e33-e34.