
بسم الله الرحمن الرحيم

EVALUATION FOR PRIMARY TMA SYNDROMES

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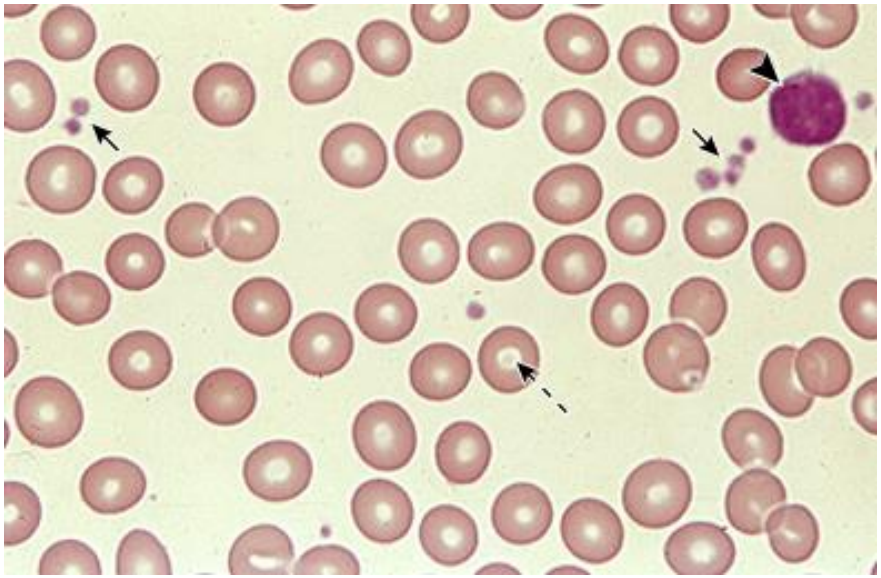
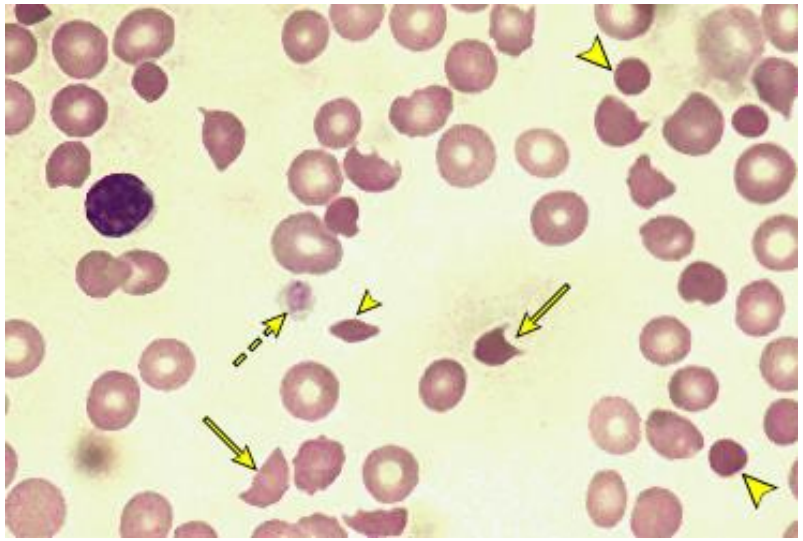
Microangiopathic hemolytic anemia (MAHA)

MAHA is a descriptive term for non-immune hemolysis (Coombs-negative hemolysis) resulting from intravascular red blood cell fragmentation that produces schistocytes on the peripheral blood smear.

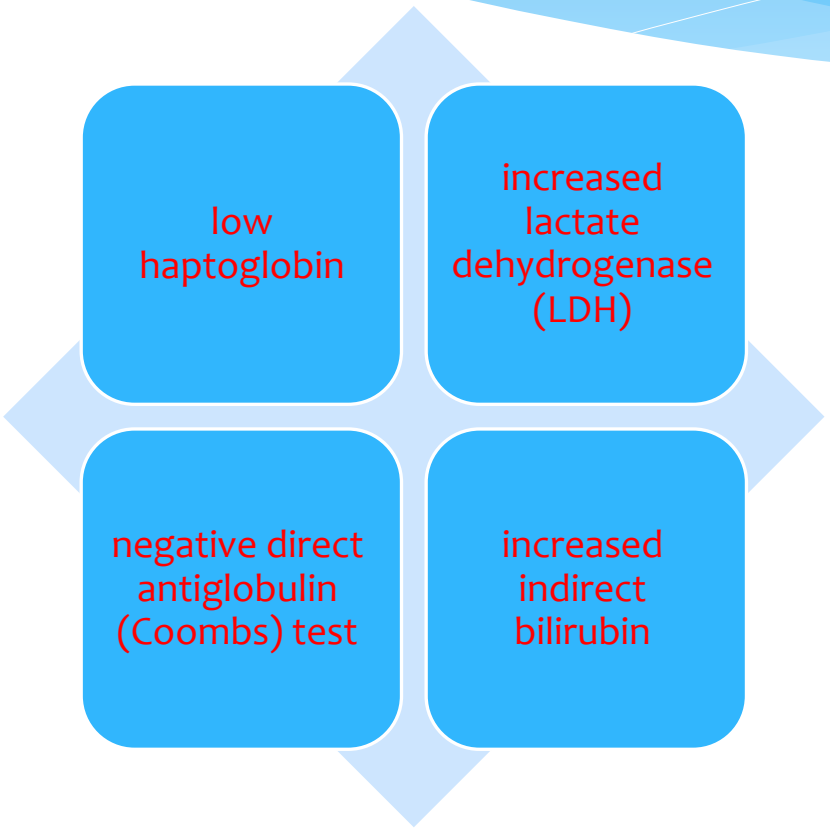
Normal peripheral blood smear



Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes



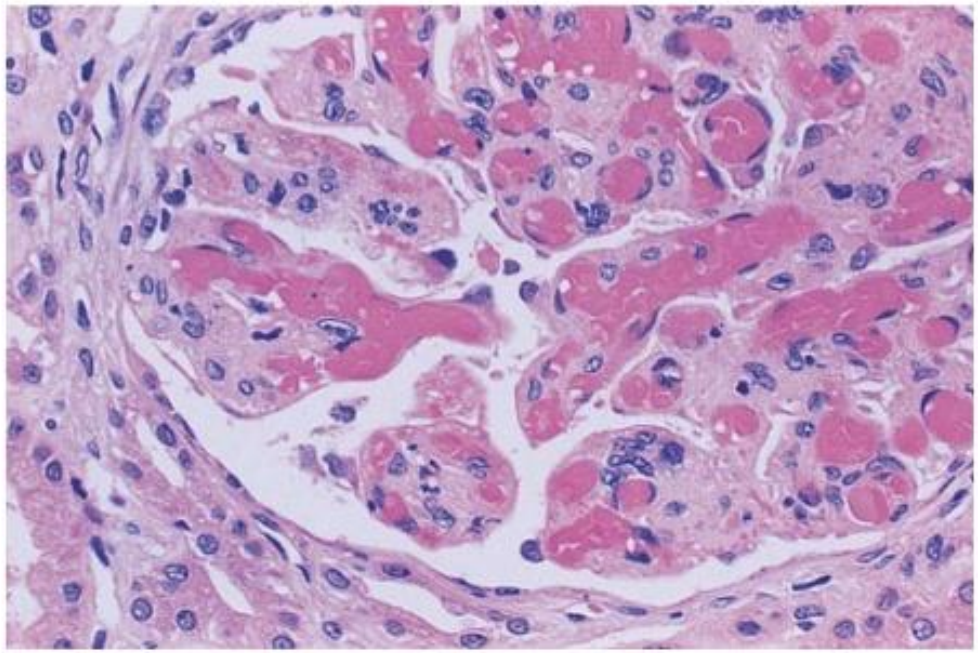
Characteristic laboratory data MAHA

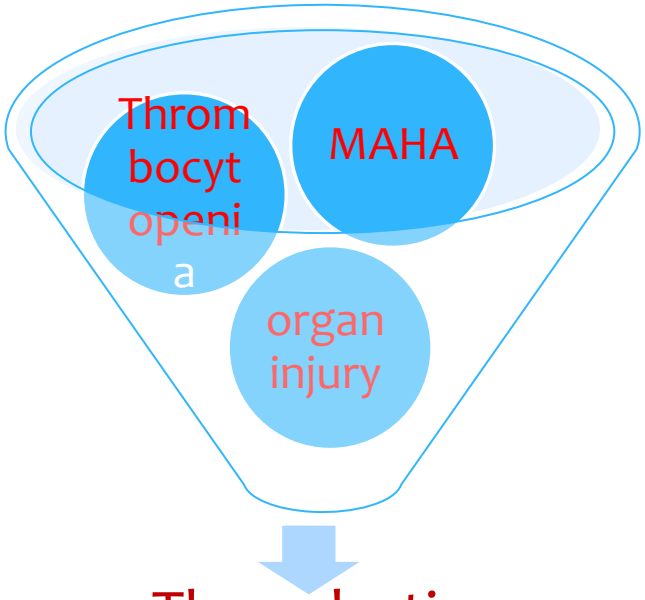


Thrombotic microangiopathy (TMA)

Specific pathologic lesion in which abnormalities in the vessel wall of arterioles and capillaries lead to microvascular thrombosis.

Renal Biopsy- Extensive glomerular capillary thrombi





Thrombotic Microangiopathy

Once MAHA and thrombocytopenia are confirmed, it is important to exclude systemic disorders as the cause of these findings.

Systemic disorders that may present with MAHA and thrombocytopenia:

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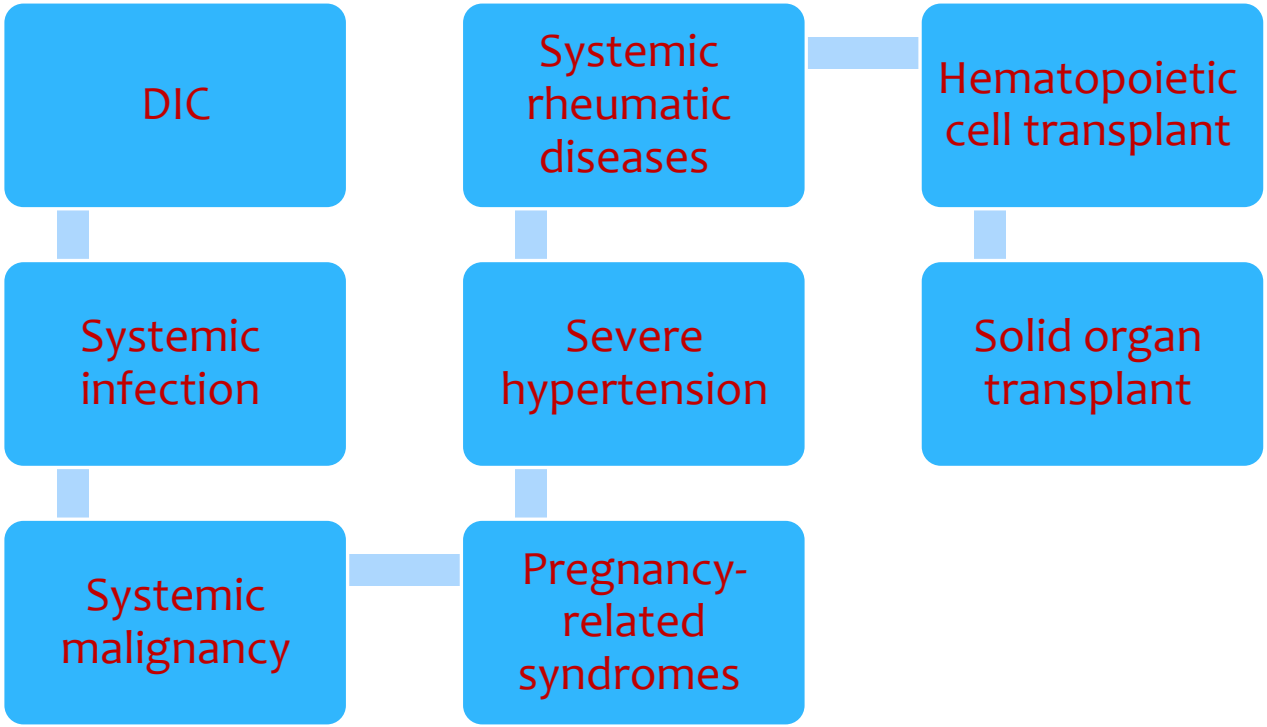

Primary thrombotic microangiopathy (TMA) syndromes

Thrombotic thrombocytopenic purpura (TTP)	Complement-mediated TMA	Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)
Inherited •	Inherited •	*Escherichia coli* •
Acquired •	Acquired •	*Shigella dysenteriae* •

Drug-induced TMA	Coagulation-mediated TMA	Metabolism-mediated TMA
• Immune-mediated • dose-related	• Inherited	• Inherited

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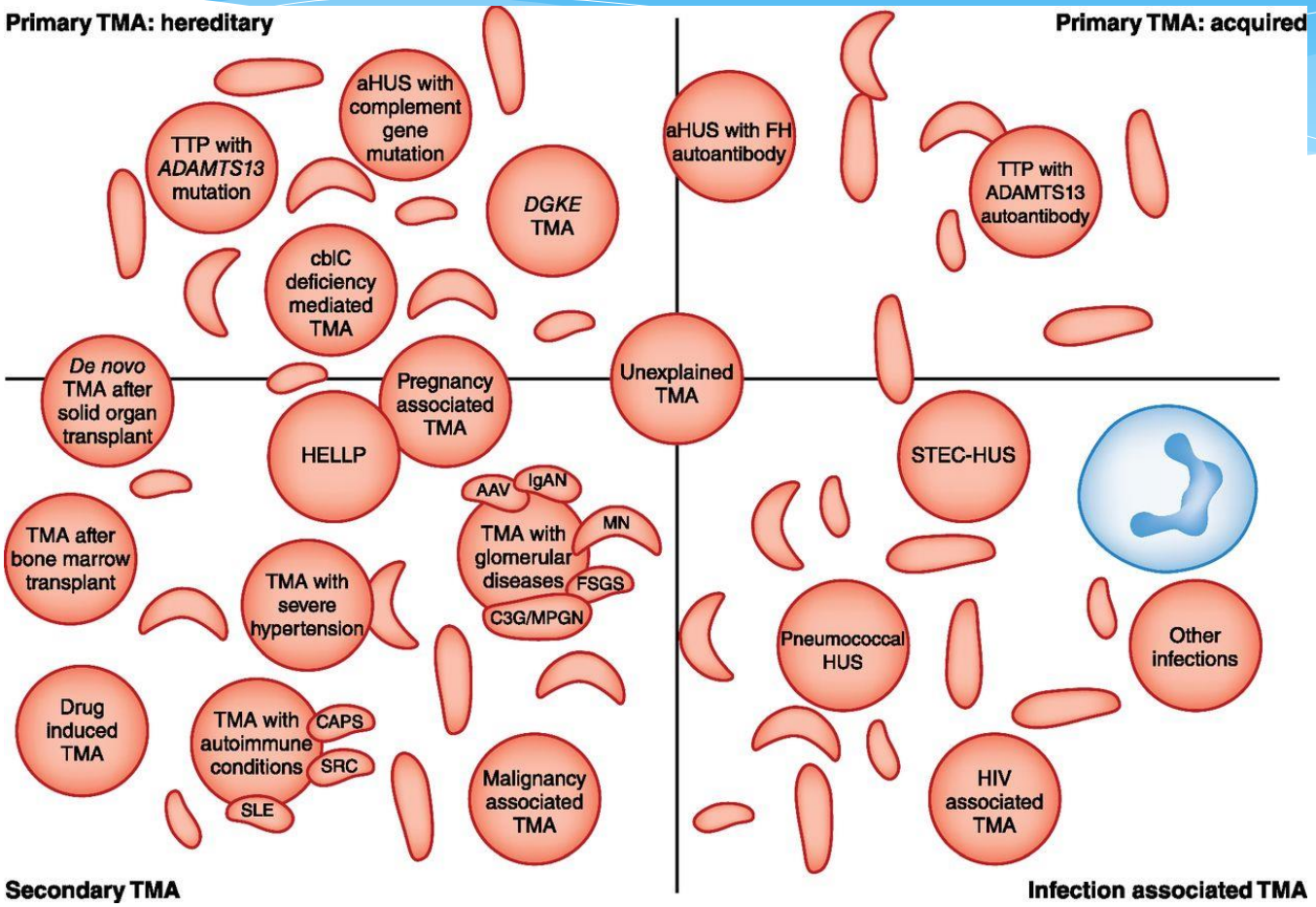
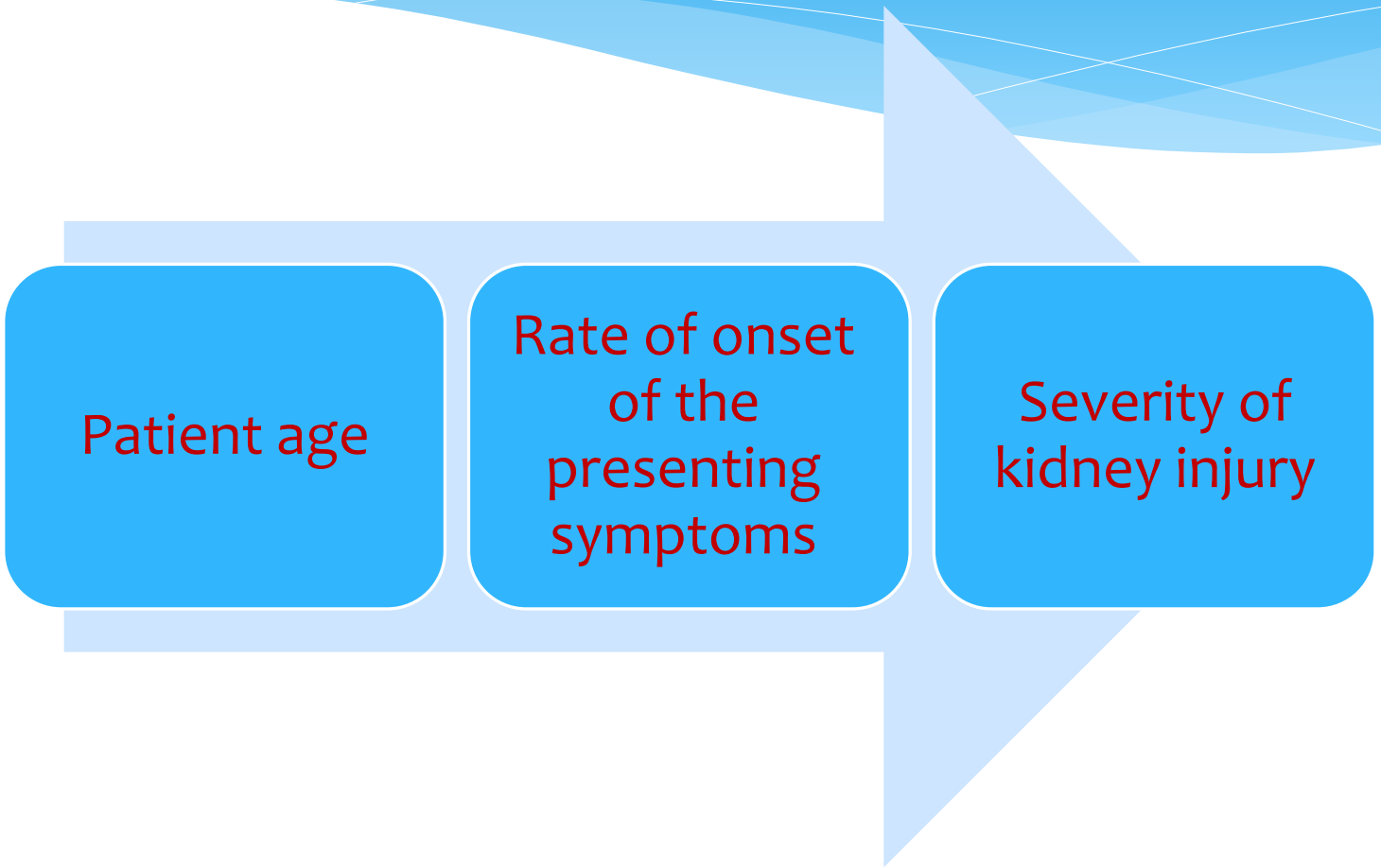
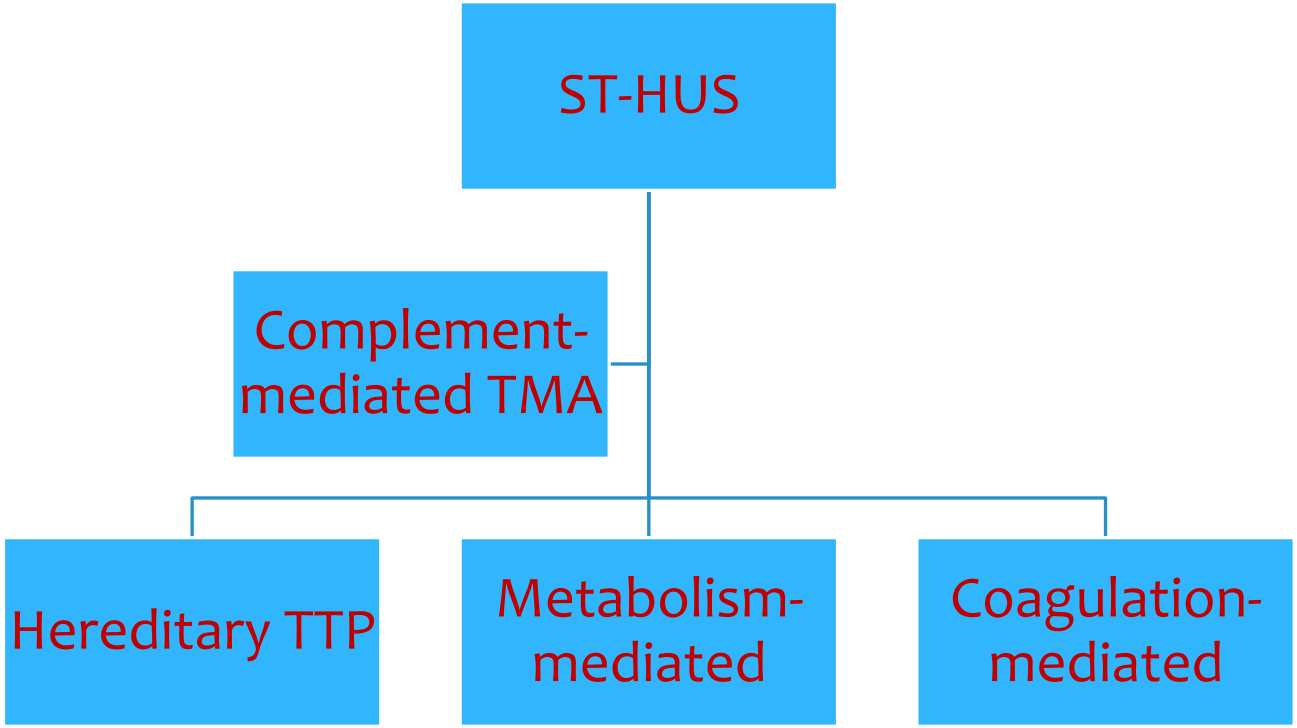


Key distinguishing features among the primary TMA syndromes:



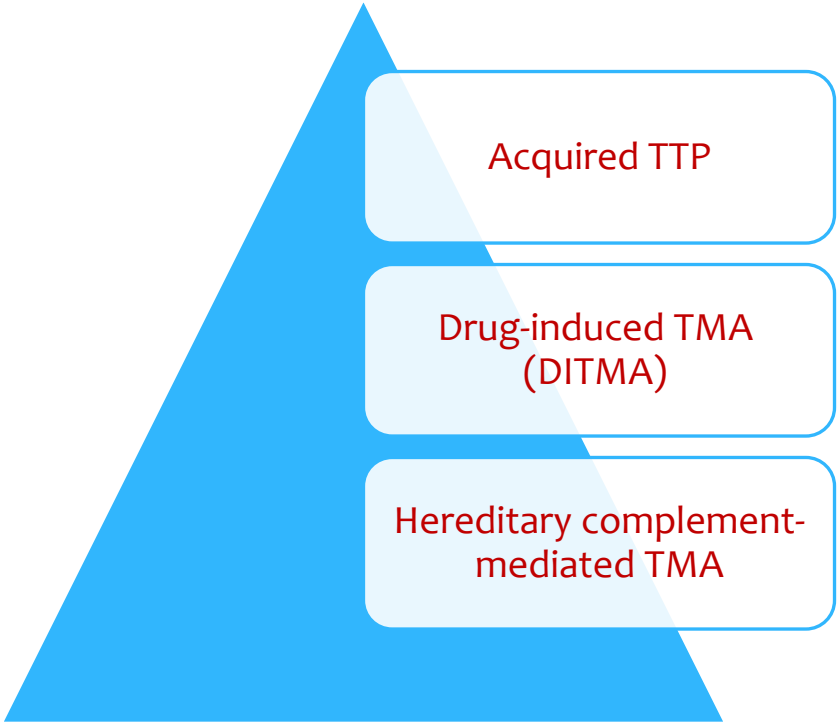
All of the primary TMA syndromes may occur at any age.

Infants/young children



Acquired TTP is rare in infants and young children.

Adults can be affected with any of the acquired or hereditary TMA syndromes



Most primary TMA syndromes present with gradually increasing symptoms over several days.

Acute, immune-mediated, drug-induced TMA is distinct; it typically has an explosive onset of severe, systemic symptoms beginning within hours of drug exposure.

In contrast, toxic, dose-dependent, drug-induced TMA may be associated with chronic kidney injury that develops over weeks or months.

Kidney injury

All of the primary TMAs can be associated with kidney Injury.

The degree of injury may be a helpful distinguishing feature.

Minimal to no kidney injury

- Hereditary or acquired TTP

Sudden, severe kidney injury

- Immune-mediated DITMA or an acute dose-dependent DITMA.

Onset of kidney injury over days

- coagulation-metabolism,complement,ST-HUS,

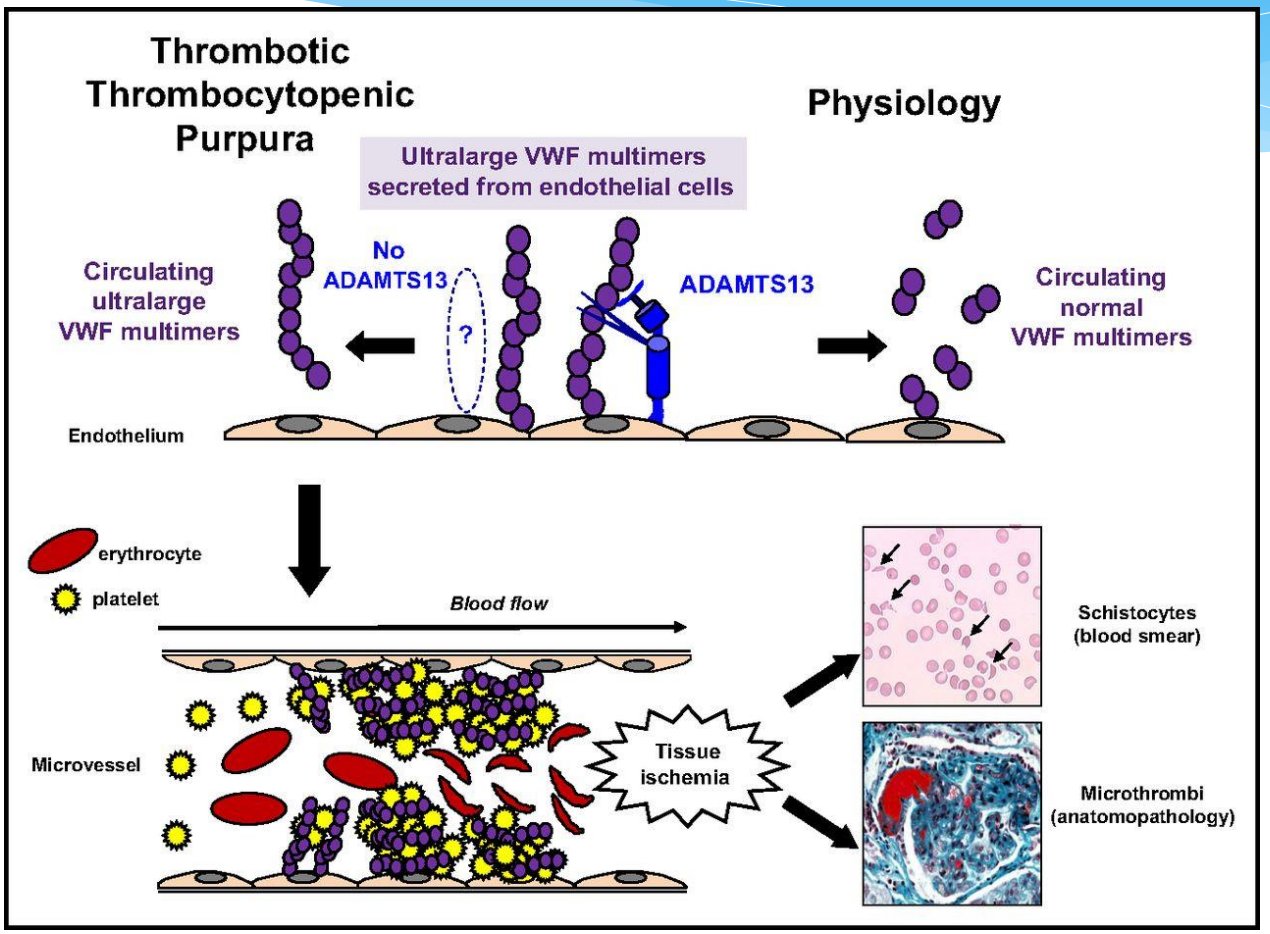
Onset of kidney injury over weeks to months

- DITMA

Features of individual primary TMAs

Thrombotic thrombocytopenic purpura (TTP)

A severe deficiency of ADAMTS13 (defined as activity <10 percent), but the diagnosis of TTP remains based on clinical judgment.


Thrombotic Thrombocytopenic Purpura
Physiology
Ultralarge VWF multimers secreted from endothelial cells
Circulating ultralarge VWF multimers
No ADAMTS13
?
ADAMTS13
Circulating normal VWF multimers
Endothelium
erythrocyte
platelet
Blood flow
Microvessel
Tissue ischemia
Schistocytes (blood smear)
Microthrombi (anatomopathology)

Deficiency of ADAMTS13

Hereditary (Upshaw-Shulman syndrome)

Acquired (inhibition of ADAMTS13 activity by an autoantibody)

* There are no specific clinical features that distinguish TTP.

* Most patients present with several days ofnonspecific symptoms, such as progressive weakness, fatigue, purpura, and gastrointestinal symptoms (eg, nausea, diarrhea).

Some patients have minimal symptoms and TTP is suspected only when anemia and thrombocytopenia are discovered.

Approximately one-third of patients have no neurologic symptoms.

One-third may have nonspecific symptoms, such as confusion and headache.

One-third will have more severe neurologic symptoms.

Patients with TTP often have minor purpura related to severe thrombocytopenia.

They rarely have overt bleeding.

Fever is uncommon.

High fever with shaking chills rarely occurs.

TTP

Minimal abnormalities of kidney function, despite microthrombi observed throughout the kidney.

Central nervous system, heart, pancreas, thyroid, adrenal glands, intestinal mucosa, and other tissues may occur.

The lungs are typically spared from ischemic injury in patients with TTP.

Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)

Abdominal pain; diarrhea (often bloody); possible history of outbreak or exposure to livestock or contaminated food, although most cases are sporadic.

Kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia occur several days after the onset of abdominal pain and diarrhea, when the initial symptoms begin to resolve.

All individuals with TMA should be investigated for STEC-HUS.

In STEC-HUS resulting in ESRD, it is recommended to screen for mutations before transplantation.

Complement-mediated TMA

The onset of complement-mediated TMA is generally sudden.

A preceding infection including a diarrheal illness may be present in up to 80 percent of children and 50 percent of adults.

Symptoms include pallor, general malaise, and poor appetite. Edema may be present. .

Complement-mediated TMA

Extra-renal manifestations are observed in up to 20 percent and include central nervous system (CNS) manifestations (the most common extra-renal finding), cardiac ischemic events, pulmonary hemorrhage and failure, pancreatitis, hepatic cytolysis, and intestinal bleeding.

Drug-induced TMA

Patients with immune-mediated drug-induced TMA (DITMA), such as DITMA due to quinine, frequently recall the exact time when symptoms suddenly began, which commonly include chills, fever, abdominal pain, diarrhea, nausea, and vomiting.

These symptoms are often attributed to an infectious illness.

Table 5. Drugs with evidence supporting a causal association with thrombotic microangiopathy[a]

Immune-Mediated TMA	Direct Drug-Induced Toxicity	Other
Quinine: Drug-dependent antibodies	Immunosuppressive agents, *e.g.*, calcineurin inhibitors: ciclosporin and tacrolimus Sirolimus IFN-α, IFN-β VEGF inhibitors, *e g.*, bevacizumab, sunitinib Chemotherapeutic agents, *e.g.*, gemcitabine, mitomycin Recreational drugs, *e.g.*, cocaine	Ticlopidine: ADAMTS13 autoantibody[b]

Drug-induced TMA

When a drug-induced etiology is suspected, potentially causative drugs are those that have been taken daily for less than two to three weeks or those taken intermittently over many years.

Quinine is the most common etiology.

Patients may have taken quinine tablets, tonic water, or bitter lemon only occasionally, and they may assume that this is not important.

Patients with some toxic, dose-related DITMA may also have sudden onset of symptoms.

An example is the intravenous injection of Opana ER (oxymorphone extended release, intended for oral use).

The history of illegal drug use or intravenous drug abuse may be difficult to obtain.

For other drugs (eg, chemotherapy medications, calcineurin inhibitors), the onset is chronic and there are no symptoms other than the gradual onset of weakness, fatigue, and symptoms related to hypertension over weeks or months.

Coagulation-mediated TMA

Hereditary deficiency of proteins involved in coagulation can cause TMA.

These syndromes differ from the abnormalities associated with hereditary thrombophilia, which cause thromboembolism in large vessels rather than systemic microvascular thrombosis.

Mutations in genes encoding thrombomodulin (TM), plasminogen, and diacylglycerol kinase epsilon (*DGKE*) have been reported to be associated with TMA .

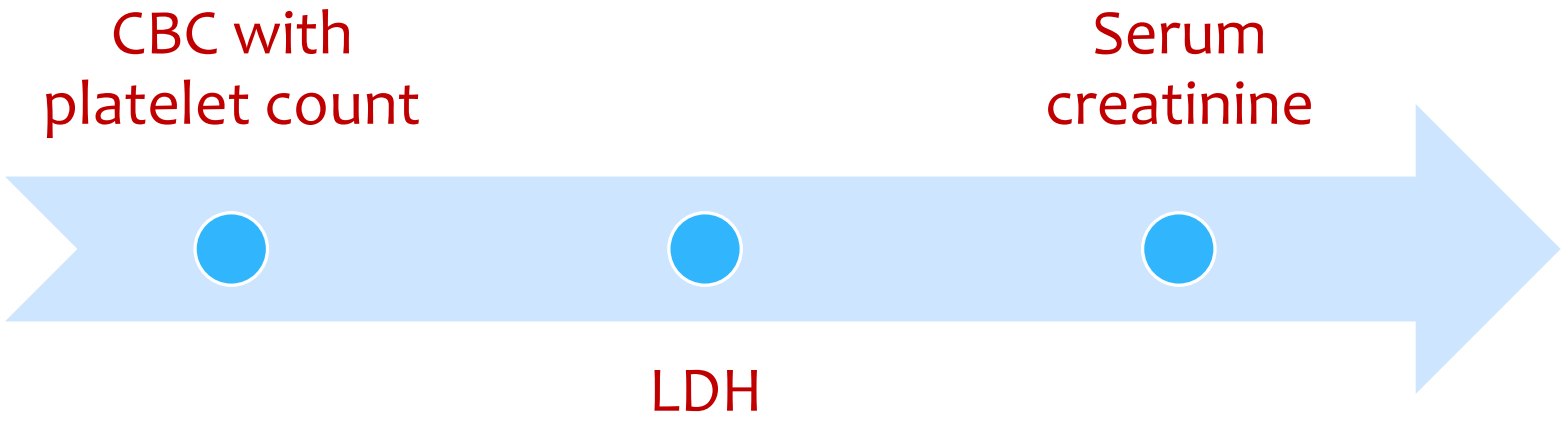
Metabolism, coagulation-mediated TMAs

Hereditary metabolism-mediated or coagulation-mediated TMAs typically occur in infants but can occur in Adults.

These disorders do not have specific presenting symptoms.

Patients may describe symptoms related to progressive kidney failure, such as weakness and fatigue.

Laboratory evaluation



All patients with microangiopathic hemolytic anemia (MAHA) and thrombocytopenia without an obvious systemic illness responsible for these findings should have measurement of ADAMTS13 activity to assess the possibility of TTP.

This is especially important in individuals with minimal or no renal function abnormalities, a common finding in TTP.

The only exception is a patient with findings that are highly suggestive of another primary TMA (eg, diarrheal illness in a young child in the midst of an ST-HUS Outbreak).

Results of ADAMTS13 activity measurements may take several days, and patients with a clinical diagnosis of TTP require urgent therapy with PEX.

If PEX was already initiated, ADAMTS13 activity can be measured on a specimen obtained after PEX was started, because severe deficiency may persist for one or more days of PEX.

In some cases, systemic disorders such as infection or malignancy may cause marked reductions in ADAMTS13 activity in the absence of TTP.

In some cases, individuals with TTP may have ADAMTS13 activity levels above the 10 percent cutoff, perhaps related to previous transfusions.

The ultimate diagnosis of TTP or another condition remains a clinical decision and cannot be based solely on ADAMTS13 activity.

Diarrhea/known infectious diarrhea exposure

All patients with MAHA and thrombocytopenia without an obvious systemic illness responsible for these findings ;

Stool culture for enterohemorrhagic *Escherichia coli*

who have had severe abdominal pain with diaarhea

who have been exposed to a known outbreak of infectious diarrhea

Should have a stool culture for enterohemorrhagic *Escherichia coli* (EHEC).

This testing requires specific culture media, distinct from the stool cultures for routine entericpathogens.

Shigella dysenteriae is a more common cause of TMA in Asia but is not a common cause in the Americas or Europe.

Testing for Shiga toxin by immunoassay is also important.

Homocysteine and MMA testing

All patients with MAHA and thrombocytopenia who have negative testing for TTP and ST-HUS (ie, patients with ADAMTS13 activity ≥10 percent and no evidence of Shiga toxin-producing enteric infection) should be tested for cobalamin C deficiency-mediated TMA .


low methionine levels
Elevated homocysteine
Methylmalonic aciduria

Role of complement testing

Decreased levels of complement factors or the presence of anti-complement factor H (CFH) antibodies may be helpful in suggesting a complement-mediated TMA.

However, normal complement levels do not eliminate the possibility of a complement-mediated TMA, and therapy cannot be based exclusively on this testing.

Role of complement testing

Children with TMA and renal insufficiency who do not have the clinical features of ST-HUS

Adults with TMA and AKI who have normal or only moderately low ADAMTS13 activity

who do not have a history indicating a drug-induced etiology

Postpartum women with rapidly progressive AKI following delivery.

complement-mediated TMA

Management is based on clinical features such as the severity and persistence of kidney injury.

Role of molecular testing

The role of additional molecular testing (eg,for *DGKE* and/or *MMACHC* mutations) is unclear.

Role of molecular testing

Children with renal insufficiency who do not have the clinical features of ST-HUS.

Adults who have normal or moderately low ADAMTS13 activity.

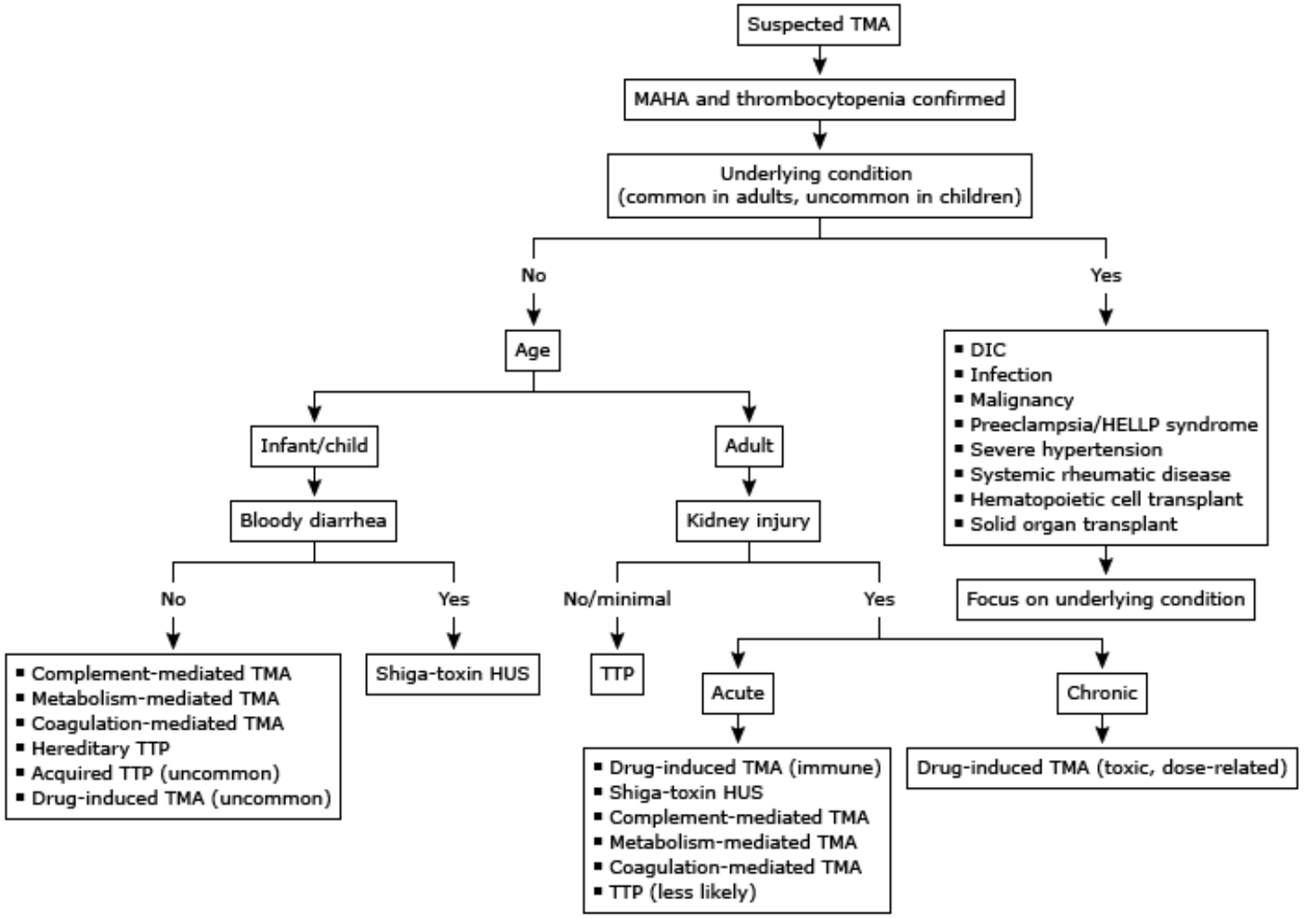
Who do not have a history indicating a drug-induced etiology.

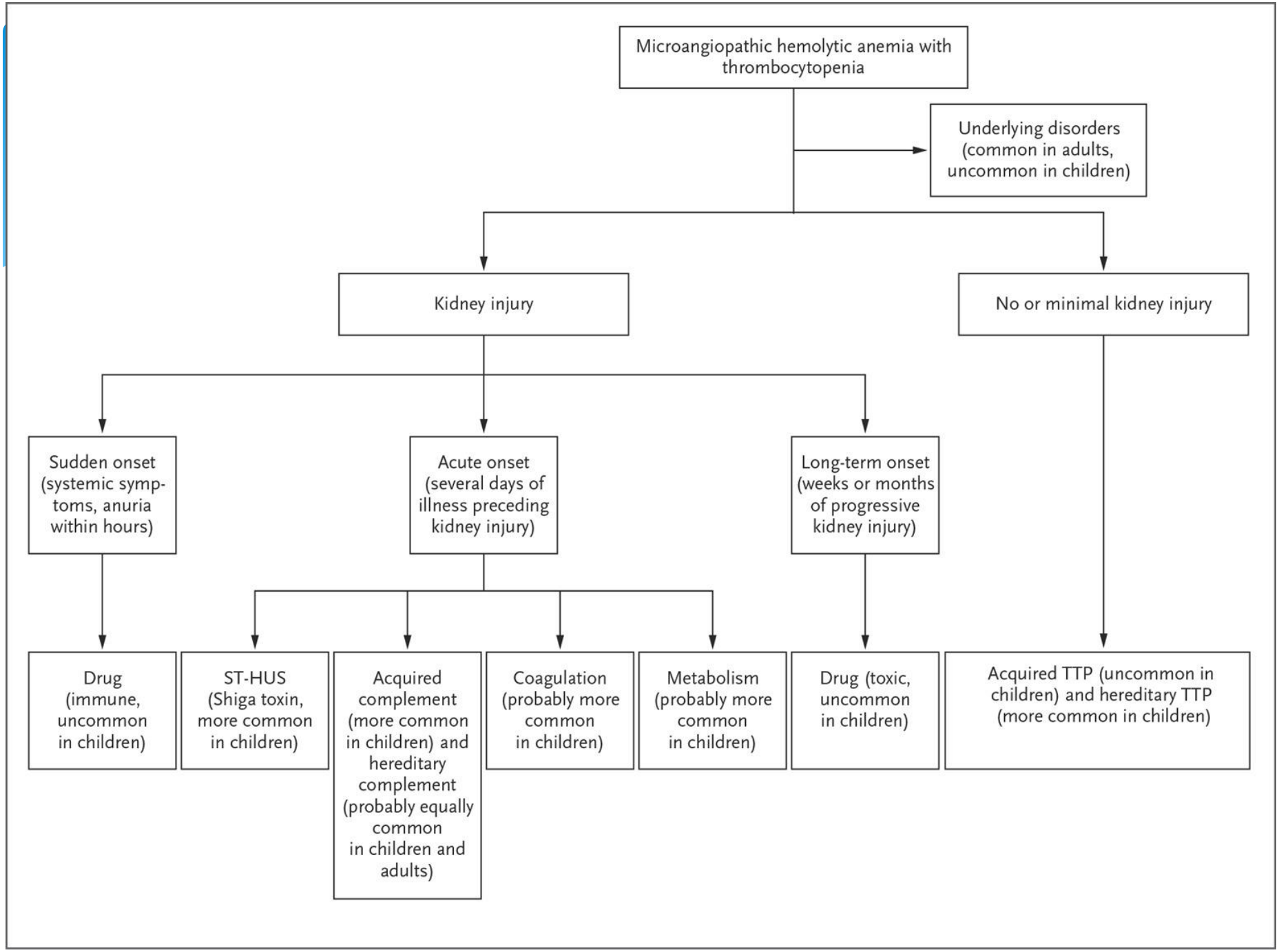
A Testing for *MMACHC* mutations should occur reflexively for individuals with TMA who have hyperhomocysteinemia/methyl-malonic aciduria.

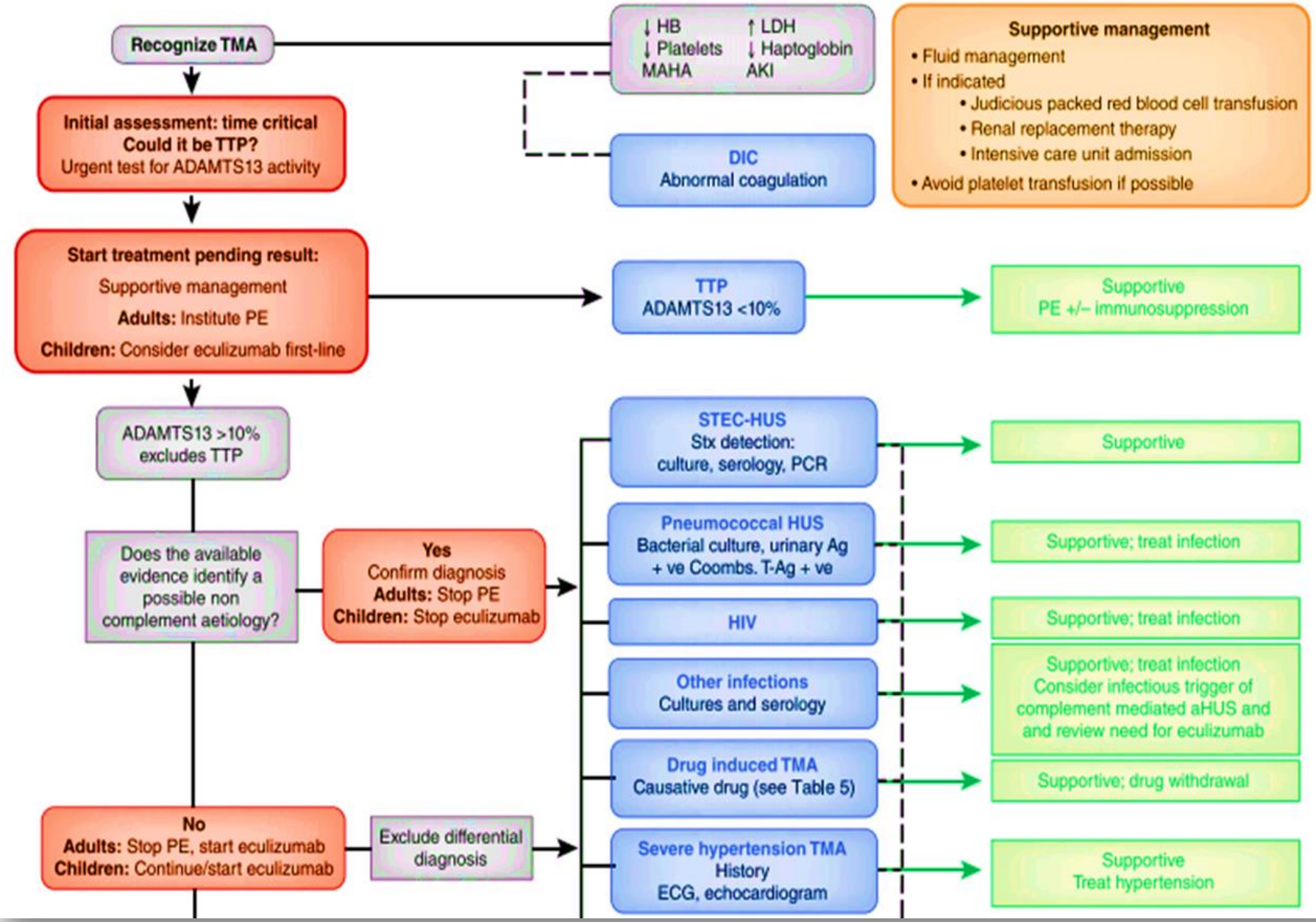
Role of kidney biopsy

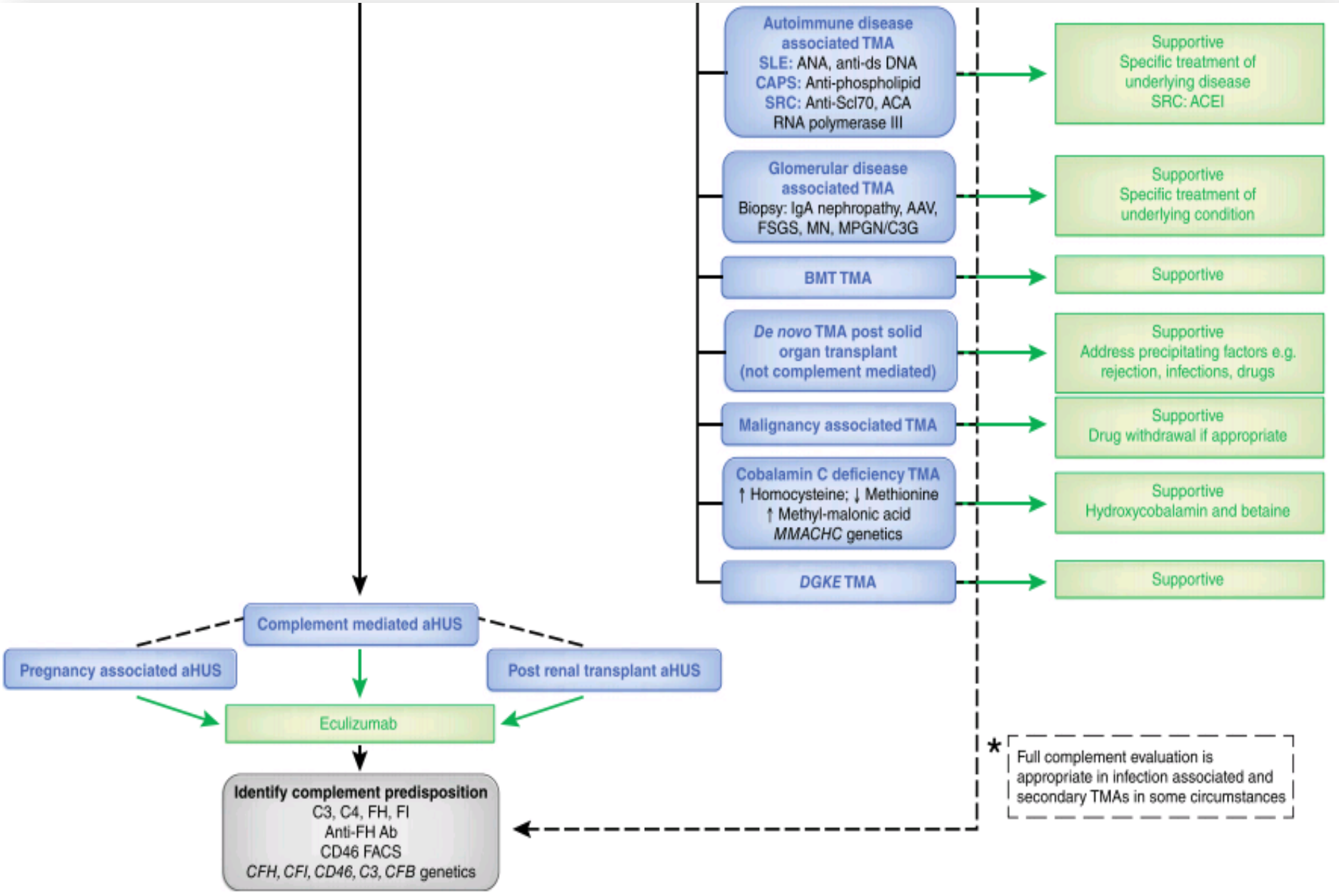
Renal biopsy is not helpful for determining the etiology of a primary TMA syndrome.

Likely causes of microangiopathic hemolytic anemia and thrombocytopenia according to presenting findings




Microangiopathic hemolytic anemia with thrombocytopenia
Underlying disorders (common in adults, uncommon in children)
Kidney injury
No or minimal kidney injury
Sudden onset (systemic symptoms, anuria within hours)
Acute onset (several days of illness preceding kidney injury)
Long-term onset (weeks or months of progressive kidney injury)
Drug (immune, uncommon in children)
ST-HUS (Shiga toxin, more common in children)
Acquired complement (more common in children) and hereditary complement (probably equally common in children and adults)
Coagulation (probably more common in children)
Metabolism (probably more common in children)
Drug (toxic, uncommon in children)
Acquired TTP (uncommon in children) and hereditary TTP (more common in children)


Recognize TMA
↓ HB ↑ LDH
↓ Platelets ↓ Haptoglobin
MAHA AKI
Supportive management
• Fluid management
• If indicated
• Judicious packed red blood cell transfusion
• Renal replacement therapy
• Intensive care unit admission
• Avoid platelet transfusion if possible
Initial assessment: time critical
Could it be TTP?
Urgent test for ADAMTS13 activity
DIC
Abnormal coagulation
Start treatment pending result:
Supportive management
Adults: Institute PE
Children: Consider eculizumab first-line
TTP
ADAMTS13 <10%
Supportive
PE +/– immunosuppression
ADAMTS13 >10%
excludes TTP
STEC-HUS
Stx detection:
culture, serology, PCR
Supportive
Does the available evidence identify a possible non complement aetiology?
Yes
Confirm diagnosis
Adults: Stop PE
Children: Stop eculizumab
Pneumococcal HUS
Bacterial culture, urinary Ag
+ ve Coombs. T-Ag + ve
Supportive; treat infection
HIV
Supportive; treat infection
Other infections
Cultures and serology
Supportive; treat infection
Consider infectious trigger of complement mediated aHUS and and review need for eculizumab
Drug induced TMA
Causative drug (see Table 5)
Supportive; drug withdrawal
No
Adults: Stop PE, start eculizumab
Children: Continue/start eculizumab
Exclude differential diagnosis
Severe hypertension TMA
History
ECG, echocardiogram
Supportive
Treat hypertension


Autoimmune disease associated TMA
SLE: ANA, anti-ds DNA
CAPS: Anti-phospholipid
SRC: Anti-Scl70, ACA
RNA polymerase III
Supportive
Specific treatment of underlying disease
SRC: ACEI
Glomerular disease associated TMA
Biopsy: IgA nephropathy, AAV, FSGS, MN, MPGN/C3G
Supportive
Specific treatment of underlying condition
BMT TMA
Supportive
De novo TMA post solid organ transplant (not complement mediated)
Supportive
Address precipitating factors e.g. rejection, infections, drugs
Malignancy associated TMA
Supportive
Drug withdrawal if appropriate
Cobalamin C deficiency TMA
↑ Homocysteine; ↓ Methionine
↑ Methyl-malonic acid
MMACHC genetics
Supportive
Hydroxycobalamin and betaine
DGKE TMA
Supportive
Complement mediated aHUS
Pregnancy associated aHUS
Post renal transplant aHUS
Eculizumab
Identify complement predisposition
C3, C4, FH, FI
Anti-FH Ab
CD46 FACS
CFH, CFI, CD46, C3, CFB genetics
* Full complement evaluation is appropriate in infection associated and secondary TMAs in some circumstances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