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Thrombotic Microangiopathy, Suspected Atypical Hemolytic Uremic Syndrome (aHUS) Order Set (Greater than 18 years of age) TMA, Thrombocytopenia, Anemia with Red Blood Cell Fragments, Hemolysis

ACTION

Initial Management

Suspect TMA if patient presents with thrombocytopenia, anemia with red blood cell fragments on blood film and markers of hemolysis; if TMA is suspected, consult a hematologist1

Lab Investigations

Initial Investigations²⁻⁴

- CBC
- Blood Film
- Reticulocyte count
- LDH
- ALT, ALP, AST
- Haptoglobin
- Bilirubin total and direct
- Coagulation screen: aPTT, INR, Fibrinogen
- Direct antiglobulin test (DAT)⁵

Target Organ Damage Lab Investigations

Evidence of target organ damage is required for a TMA diagnosis; renal involvement may indicate aHUS3

- Electrolytes
- Amylase
- Urine R + M
- BUN
- Lipase
- Urine albumin: creatinine ratio
- Creatinine
- Troponin

Additional Lab Investigations^{3,4,6}

- Ca
- Ferritin
- Uric acid
- Blood C + S
- Serum β HCG
- Mg
- Vitamin B12
- TSH
- Sputum C + S
- Urine β HCG
- Phosphate
- CK
- Serum Drug Screen
- CSF C + S
- Albumin
- C-Reactive Protein
- Urine Drug Screen
- Urine C + S
- Group + Screen
- D-dimer
- HIV serology
- Group + Screen + Crossmatch for _____ unit(s) red blood cells

Hepatitis serology for:

- HBsAg
- anti-HBs
- anti-HBc IgM
- anti-HBc
- anti-HBc (total)
- anti-HCV

Diagnostics

Ensure appropriate diagnostic tests are ordered to rule out other diagnoses, e.g. endocarditis, malignancy

- ECG⁶
- Abdominal Ultrasound with Doppler of renal artery
- CT⁶ _____ Reason: _____
- Echocardiogram⁶ _____ Reason: _____

Supportive Management

IV Therapy

- Insert peripheral IV
- IV Fluid: _____ at _____ mL/h

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Supportive Management Continued...

Blood and Blood Product Transfusion

Platelet transfusion may worsen the TMA and should be avoided unless life, organ or limb-threatening bleeding

Red blood cell transfusion is to be administered only if indicated, e.g. low hemoglobin and patient symptomatic

ADAMTS13 testing is to be done prior to transfusing any plasma-containing blood component

If applicable, prescriber to complete the following as applicable:

- Blood Products Administration Order Set
- Red Blood Cell Administration Order Set

Differential Diagnosis

Note: Consider the following investigations to help determine a specific diagnosis

Specimen for ADAMTS13 testing is to be collected prior to transfusing any plasma containing blood component. If suspect TTP, do not delay treatment (plasma infusion or plasma exchange while awaiting results)

All patients with diarrhea should have stool collected and tested for Shiga toxin

aHUS ⁷	<input checked="" type="checkbox"/> C3, C4	<input type="checkbox"/> aHUS genetics screen
TTP ⁷	<input type="checkbox"/> ADAMTS13 Activity	<input type="checkbox"/> ADAMTS13 Antibody/Inhibitor
STEC-HUS ³	<input type="checkbox"/> Stool C + S	<input type="checkbox"/> Serum PCR for Shiga toxin ³
Pneumococcal HUS ⁷	<input type="checkbox"/> Urinary Antigen	<input type="checkbox"/> T activation
Systemic lupus erythematosus (SLE) ⁷	<input type="checkbox"/> ANA	<input type="checkbox"/> Anti-dsDNA
Scleroderma renal crisis (SRC) ⁷	<input type="checkbox"/> ENA panel	<input type="checkbox"/> Anti-Scl-70
Cobalamin C disease ⁷	<input type="checkbox"/> Plasma homocysteine level <input type="checkbox"/> Urine methylmalonic acid level	<input type="checkbox"/> Plasma methylmalonic acid level <input type="checkbox"/> Genetic testing for MMA+HCU
Autoimmune vasculitis ⁷	<input type="checkbox"/> ANCA	<input type="checkbox"/> anti-GBM
Other	<input type="checkbox"/> _____	<input type="checkbox"/> _____

Note: Consider the following differential diagnoses and appropriate investigations prior to treating TMA

Bacterial endocarditis ⁴	Echocardiogram; Blood C + S
Disseminated malignancy ⁷	Age appropriate cancer screening
Malignant hypertension ⁷	Systolic BP greater than 200 mmHg
HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets); Preeclampsia ^{4,8}	Pregnant (Serum/Urine β HCG) or postpartum; ALT, ALP, Bilirubin; AST; LDH; APTT, INR, Fibrinogen
DIC (Disseminated Intravascular Coagulation) ⁴	aPTT, INR, Fibrinogen; D-dimer
Catastrophic antiphospholipid syndrome (CAPS) ⁷	Anti-beta-2 Glycoprotein 1; Lupus Anticoagulant Assay; Anticardiolipin Antibodies

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Consults

Consult nephrology if need for urgent dialysis, e.g. acute hyperkalemia, volume overload

- | | |
|---|---|
| <input type="checkbox"/> Hematologist - Reason: _____ | <input type="checkbox"/> Neurologist - Reason: _____ |
| <input type="checkbox"/> Infectious Diseases Specialist - Reason: _____ | <input type="checkbox"/> Obstetrician - Reason: _____ |
| <input type="checkbox"/> Internal Medicine Specialist - Reason: _____ | <input type="checkbox"/> Pharmacist - Reason: _____ |
| <input type="checkbox"/> Nephrologist - Reason: _____ | <input type="checkbox"/> _____ - Reason: _____ |

Disposition

Treatment with plasma exchange requires transfer to an apheresis centre

Treatment with eculizumab requires oversight by a centre with experience in treating aHUS

- Arrange transport by EMS to apheresis centre STAT as per policy/procedure

Additional Orders

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Order Set Development and Implementation Considerations

Abbreviations

A Disintegrin and Metalloproteinase with a Thrombospondin Type 1 Motif, Member 13 = ADAMTS13	
Anti-glomerular basement membrane= anti-GBM	Antineutrophil cytoplasmic antibodies = ANCA
Emergency Medical Services = EMS	Hemolytic Uremic Syndrome = HUS
Methylmalonic Acidemia with Homocystinuria = MMA+HCU	Thrombotic Microangiopathy = TMA
Shiga Toxin Escherichia Coli = STEC	Thrombotic Thrombocytopenic Purpura = TTP

The intent of this Order Set Development and Implementation Considerations section is to provide additional information for Order Set Committees and/or Order Set leads when implementing this order set locally. This section is not designed to be included in the actual order set and can be removed if needed.

Patient Care Considerations

- **Disseminated Intravascular Coagulation (DIC):** The clinical picture of TMAs and DIC is very similar and must be distinguished to allow for appropriate management and treatment.³ TMA occurs in the context of normal INR and aPTT values, whereas these values, as well as D-dimer, are elevated in DIC.^{3,4}
- **Eculizumab⁷:** Eculizumab is the recommended therapy if complement-mediated aHUS is presumed and TTP is excluded. As Eculizumab is not universally available, it is often not prescribed until there is enough evidence to assume aHUS (i.e. ADAMTS13 > 10%). In adults, plasma exchange is usually the initial therapy after TMA diagnosis until aHUS can be identified or if Eculizumab is not available.
- **Malignant Hypertension³:** Malignant hypertension is an example of a complementing-activating condition. In patients with malignant hypertension, renal function should improve once blood pressure is under control. If there is persistence of renal injury, anemia and thrombocytopenia after blood pressure control, a diagnosis of aHUS unmasked by the malignant hypertension should be considered.
- **Plasma Exchange⁷:** Plasma exchange is the initial treatment of choice until ADAMTS13 activity result is available to exclude TTP and should be started as soon as TMA is suspected. If plasma exchange is not available at a facility, patients with suspected TMA should be transferred to an apheresis centre as soon as possible.
- **Pneumococcal HUS⁷:** "TMA may occur in adults and children in the context of invasive *Streptococcus pneumoniae* infection, and the high morbidity and mortality rate usually reflects the severity of the infection." Supportive management and treatment of the infection are the focus for this type of TMA.
- **Shiga Toxin-Producing *E. coli* HUS (STEC-HUS)^{3,9}:** STEC-HUS is one of the major TMAs and predominately affects children 5 years and younger. It is diagnosed by revealing a positive stool or rectal swab sample positive for *E. coli* through culture or PCR. Any patient presenting with TMA like symptoms and diarrhea should be tested for STEC-HUS, regardless of age.
- **Syndrome of Hemolysis, Elevated Liver Enzymes and Low Platelets (HELLP):** Presentation of HELLP syndrome can be similar to aHUS, however, there are no coagulation abnormalities in aHUS and liver transaminases are less elevated in aHUS than in HELLP syndrome.⁸ Maternal condition will improve in those with HELLP syndrome following delivery, where it will not in aHUS.^{4,8}
- **Thrombotic Thrombocytopenic Purpura (TTP):** TTP is one of the major TMAs and its clinical presentation is often indistinguishable from aHUS and STEC-HUS.⁹ Pathologically it differs from HUS, which can be identified through ADAMTS13 activity measurement. TTP can be identified by an ADAMTS13 reduction of less than 5 to 10% of normal activity level.^{3,9} It is important that blood for ADAMTS13 testing is collected prior to initiating plasma exchange, however, awaiting test results should not delay initiation of treatment.⁷ If the ADAMTS13 test results show greater than 10% of normal activity, this often excludes TTP and aHUS should be considered.⁷ Values that are low but higher than 10%

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ACTION

require consultation with an expert in TTP/aHUS to determine next steps, especially if ADAMTS13 was collected after plasma or platelet transfusion.

- **TMA Associated with Autoimmune Diseases**⁷: TMA can occur in association with a variety of autoimmune diseases, including: systemic lupus erythematosus (SLE), cryopyrin-associated periodic syndromes (CAPS) and scleroderma renal crisis (SRC). For SLE, CAPS, and SRC with TMA, treatment should be of the underlying condition, making it important to perform the appropriate tests and assessments to properly diagnose patients.
- **Vitamin B12**: Vitamin B12 deficiency with the appearance of fragments and neurological symptoms can mimic TMAs and serum B12 levels and LD are to be tested prior to initiating treatment for HUS or TTP.⁴

References

Key References¹⁻⁹ Other References¹⁰

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