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| **PROTOCOL TITLE:** Kidney and Pancreas Post-transplant Management of DeNovo Thrombotic Microangiopathy (TMA) |
| **APPLICABLE FACILITIES:**[ ] EHC [ ] EDH [ ] EHH [ ] EHI [ ] EHN [ ] EJCH [ ] ELTAC [ ] ESJH[x] EUH [ ] EUHM [ ] EUHS [ ] EUOSH [ ] EWWH [ ] RJV-ERH [ ] RJV-ESOP [ ] TEC/ESA |
| **EFFECTIVE DATE:**  | **ORIGINATION DATE:** 10/20/2020 |

**CATEGORY:** Diagnostic/Therapeutic/Preventive

**LEVEL:** Independent

**Definition**

De novothrombotic microangiopathy (TMA) is a rare post-transplant complication that can lead to significant morbidity and mortality. TMA can occur at any time post-transplant, although most commonly within the first 3-6 months. The incidence of de novoTMA has been reported to be 1.5%-14% with an estimated graft loss rate of 40% within two years of diagnosis. There are many potential precipitating factors, including but not limited to calcineurin inhibitor (CNI) use, mTOR inhibitor use, antibody-mediated rejection (AMR), viral infection and antiviral medication use. Although drug-associated TMA can occur regardless of trough levels, it has been reported that patients with drug-associated TMA have higher trough levels compared to patients without. Patients on combination mTOR and CNI regimens have also been found to be at higher risk of developing TMA.

**Diagnosis**

TMA should be suspected in transplant patients with progressive graft dysfunction due to unknown cause as well as anemia and thrombocytopenia. Definitive diagnosis requires biopsy.

**Workup**

Initial workup-

* + Bilirubin (increased), Coombs testing (negative), haptoglobin (decreased/absent), lactate dehydrogenase (LDH) (elevated)
	+ Aspartate aminotransferase (AST)/alanine aminotransferase (ALT), creatinine
	+ Prothrombin time (PT)/partial thromboplastin time (PTT)/d-dimer – usually normal
	+ CBC – demonstrates thrombocytopenia (typically <30 X 109/L)
	+ Blood smear – red blood cell fragmentation (schistocytes), high reticulocyte count (>120 X 109/L)
	+ Antinuclear antibodies (ANA)
	+ Stool culture
	+ Shiga toxin stool polymerase chain reaction (PCR) – for patients presenting with diarrhea
	+ Complement testing if aHUS suspected
	+ *ADAMTS13* testing to r/o TTP

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* ADAMTS12 activity/Inhibition test/antibody test/sequencing test
* TMA profile aHUS/TTP C3, C4, Factor H, Factor H autoantibody, Factor I, Factor B

*Loss of function mutations in complement regulatory proteins Factor H (CFH), Factor H-related 5 (CFHR5), Factor I (CFI), Membrane Cofactor Protein / CD46 (CD46), and Thrombomodulin (THBD), as well as gain of function mutations in alternative pathway components Factor B (CFB) and C3 (C3) have all been identified in patients with atypical HUS.  Includes sequence analysis of ADAMTS13, C3, C4BPA, CD46 (MCP), CD59, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, DGK, MMACHC, PLG, THBD and deletion/duplication analysis of CFHR1 and CFHR3 via MLPA. Also includes analysis of variants c.2653C>T and c.2654G>A in the C5 gene, which are associated with poor response to eculizumab.*

* If eculizumab is considered- terminal complement pathway activity needs to be ordered (CH50, C5a and sC5b-9)

**Management**

1. **Early TMA: less than 9 months post-transplant on Bela protocol**
	1. Discontinue CNI immediately
	2. Bela continue per protocol
	3. Initiate sirolimus and maintain a trough 5-8 during the first month post-transplant and then transition to 3-5
	4. Initiate PLEX for at least 5 days, monitor for improvement in thrombocytopenia -> anemia -> UOP -> allograft function over 3-5 days
		1. Give bela 10 mg/kg at the end of the third and fifth sessions, and after every 2-3 sessions thereafter if PLEX continued
2. **Early TMA: less than 9 months post-transplant on tac protocol**
	1. Discontinue CNI immediately
	2. Bela
		1. Ok to consider Bela for relative contraindications (HIV, CMV high risk, KP)
		2. Do not use Bela for absolute contraindications i.e. EBV negative
		3. Dose bela per package insert: Belatacept 10 mg/kg IVPB on day 1, day 5, day 14, month 1, month 2, and month 3. Reduce to 5mg/kg IVPB beginning month 4 and continue monthly thereafter
	3. Initiate sirolimus and maintain a trough 3-5
3. **Late TMA: more than 9 months post-transplant on Bela protocol**
	1. Discontinue CNI immediately
	2. Bela continue per protocol
	3. Initiate PLEX for at least 5 days, monitor for improvement in thrombocytopenia -> anemia -> UOP -> allograft function over 3-5 days
		1. Give bela 10 mg/kg at the end of the third and fifth sessions, and after every 2-3 sessions thereafter if PLEX continued
4. **Late TMA: more than 9 months post-transplant on tac protocol**
	1. Discontinue CNI immediately
	2. Bela
		1. Ok to consider Bela for relative contraindications (HIV, CMV high risk, KP)
		2. Do not use Bela for absolute contraindications i.e. EBV negative
		3. Dose per package insert: Belatacept 10 mg/kg IVPB on day 1, day 5, day 14, month 1, month 2, and month 3. Reduce to 5mg/kg IVPB beginning month 4 and continue monthly thereafter
	3. Initiate PLEX for at least 5 days, monitor for improvement in thrombocytopenia -> anemia -> UOP -> allograft function over 3-5 days
		1. Give Bela 10 mg/kg at the end of the third and fifth sessions, and after every 2-3 sessions thereafter if PLEX continued
5. Absolute Contraindications for Bela
	1. Start sirolimus and continue on 5-8 trough
6. **Plasmapheresis (PLEX):** Ensure TMA send out labs are sent before initiating PLEX
	1. Initiate PLEX for 5 days, monitor for improvement in thrombocytopenia -> anemia -> UOP ->allograft function over 3-5 days
		1. Give bela 10 mg/kg at the end of the third and fifth sessions, and after every 2-3 sessions thereafter if PLEX continued
7. **Eculizumab**
	1. Can be considered in patients with:
		1. Plasmapheresis-dependence and/or no improvement after 5 days of PLEX
		2. Laboratory confirmed genetic disorder
	2. Eculizumab is non-formulary due to high cost and requires submission of P&T non-formulary request form. Drug will be ordered as patient specific supply pending approval and typically takes 1-2 business days for delivery.
	3. Recommended dosing of Eculizumab: 900mg weekly x 4 weeks, followed by 1200mg at week 5 then 1200mg q2 weeks thereafter.
	4. NOTE: **eculizumab is removed by plasmapheresis** and patients require supplemental doses after plasmapheresis therapy. **Consider discontinuing plasmapheresis if eculizumab is initiated.**
	5. Eculizumab may be discontinued when TMA is clinically resolved and renal function stabilized and the absence of genetic abnormality.
	6. Patients receiving eculizumab are at increased risk of meningococcal infections and infections with encapsulated organisms. Patients should receive meningococcal vaccinations if not previously vaccinated (MenACWY and MenB) when possible AND remain on penicillin prophylaxis 500mg q12h until at least 2 weeks after final dose of eculizumab. Patients should also be up to date on pneumococcal vaccines.
		1. In case of a penicillin allergy, ciprofloxacin 500mg daily is recommended, renally adjusted if applicable.

**RELATED POLICIES / PROCEDURES:** N/A

**DEFINITIONS:** N/A

**REFERENCES AND SOURCES OF EVIDENCE:**

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**KEY WORDS:** Thrombotic microangiopathy, TMA