Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Thrombotic Microangiopathies (TTP/aHUS)

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Disclosures

- Research support from Sanofi Genzyme

Outline

- Case-based
- Differential of Thrombotic Microangiopathies
- Brief Review of Pathogenesis
- Management
  - Diagnosis
  - Treatment
  - Follow-up

Case #1

23 yo F presents with dyspnea, fatigue and petechiae

8.2	**8.9**	**8**
	26	

137	107	15
3.8	22	1.06

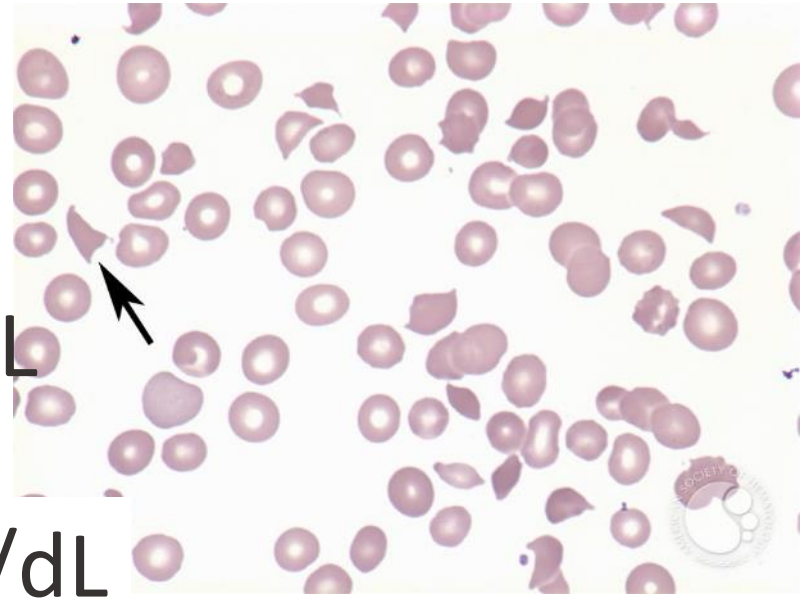
PT 12 s

PTT 32 s

Fibrinogen 250 mg/dL

LDH 865 U/dL

Haptoglobin <30 mg/dL



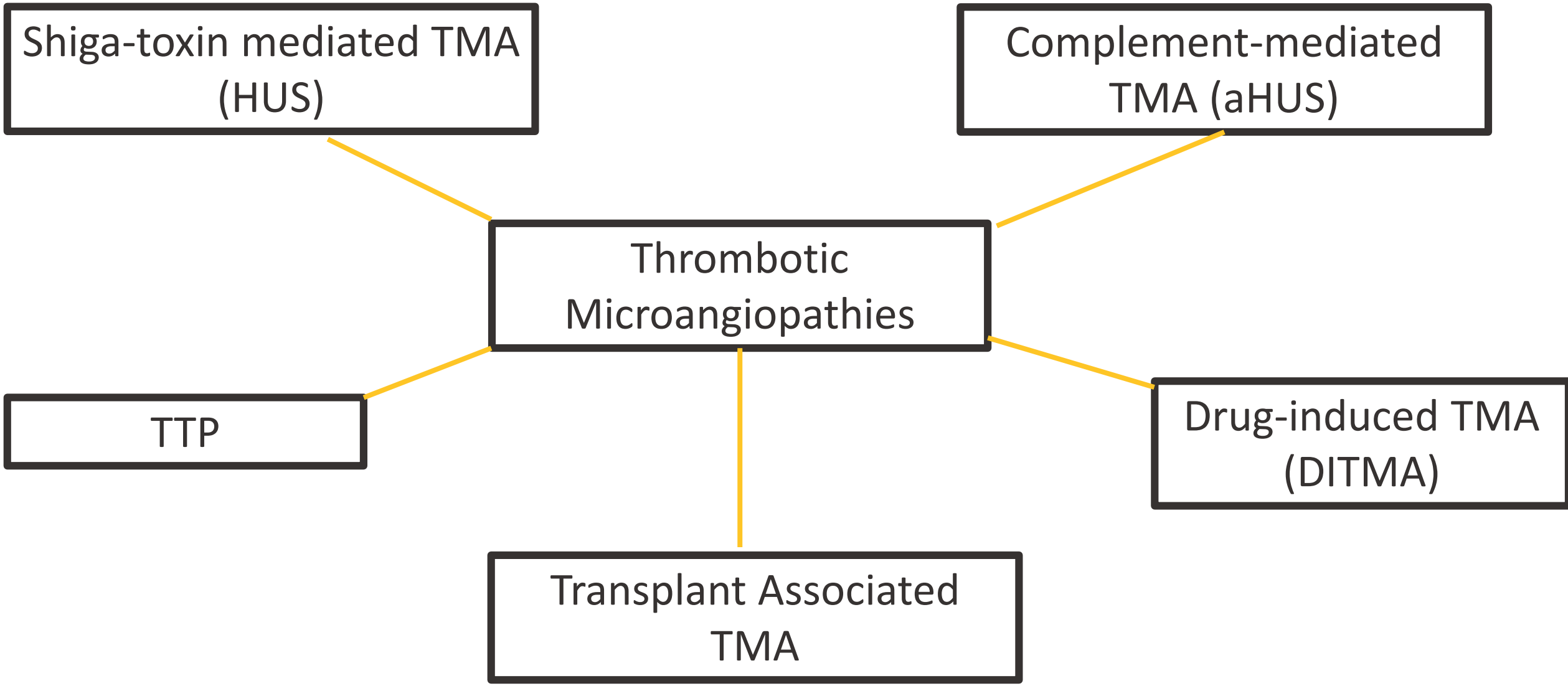
Authors: Peter Maslak; Lisa Southern;

ASH | Image Bank

Thrombotic Microangiopathies-*Diagnosis*

- Hemolytic Anemia
  - ↓HgB + ↑LDH + ↓haptoglobin
- Thrombocytopenia
- +/- renal dysfunction
- Neurologic Symptoms

TMA-*Types*


Shiga-toxin mediated TMA (HUS)
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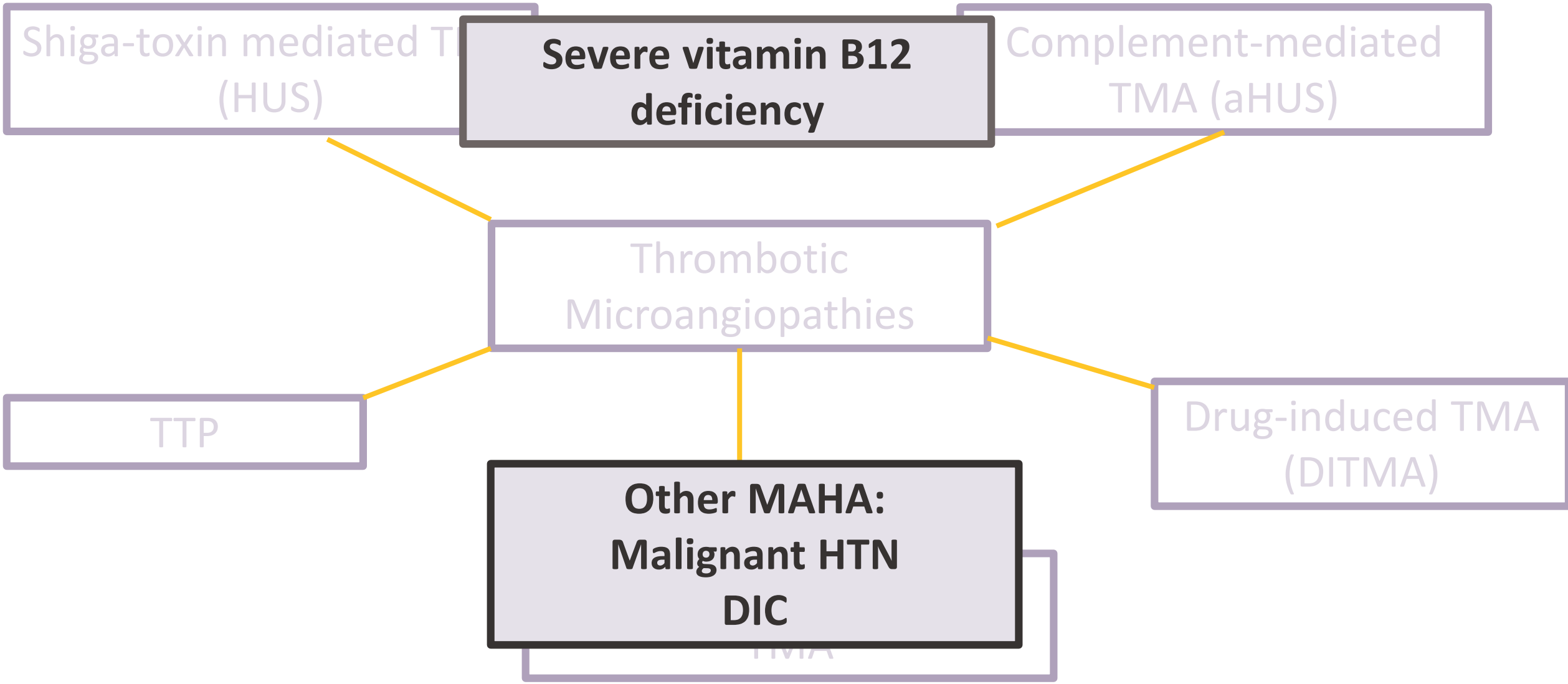
TMA-*Mimickers*



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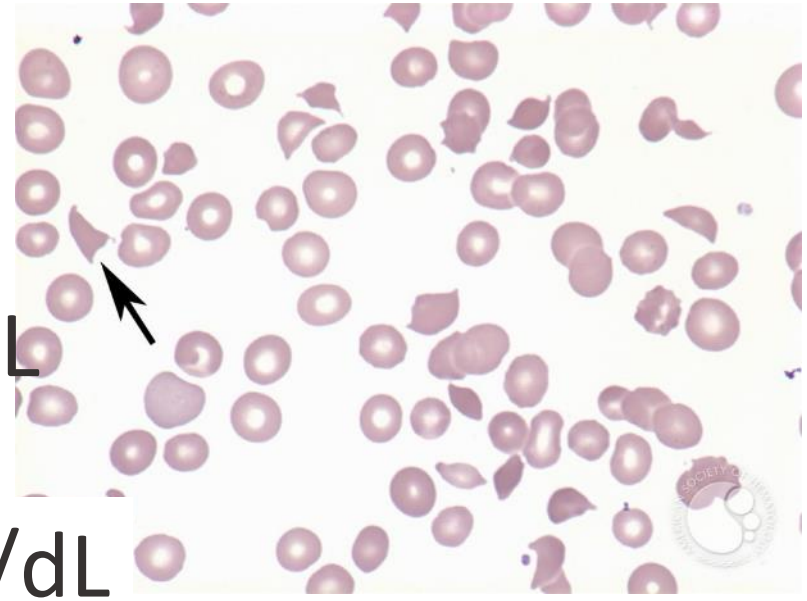

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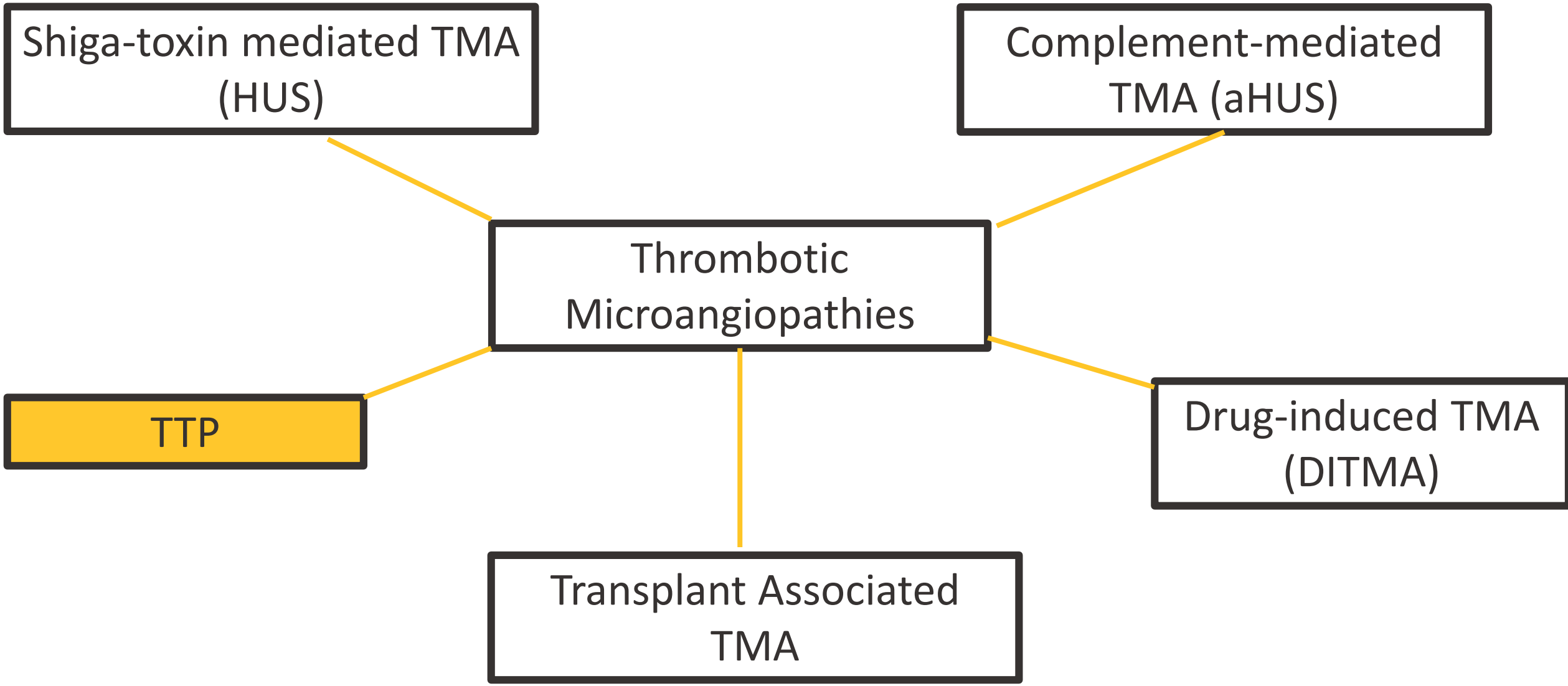
PLEX initiated…….

ADAMTS13 <10%

TMA-*Types*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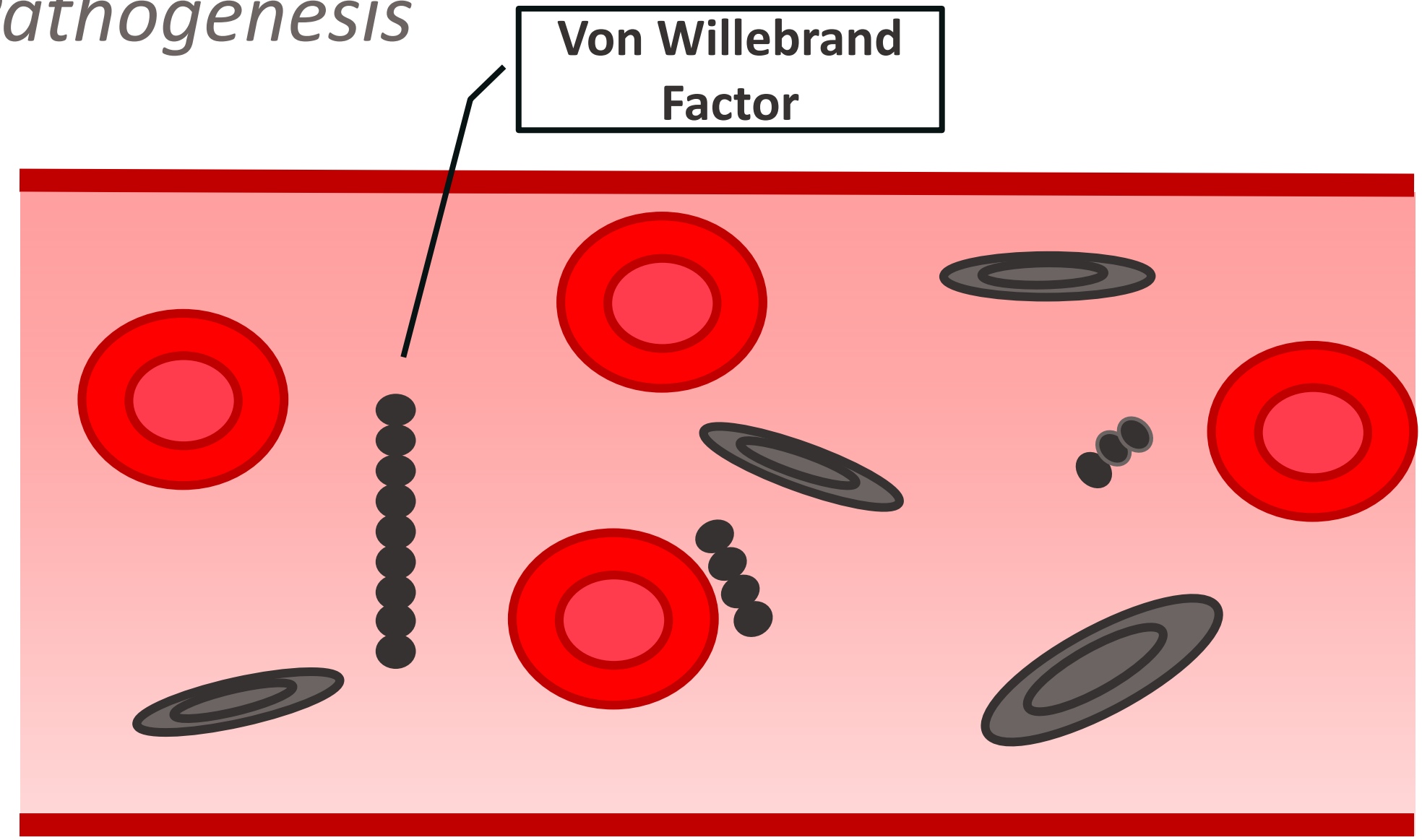
TTP: *Pathogenesis*



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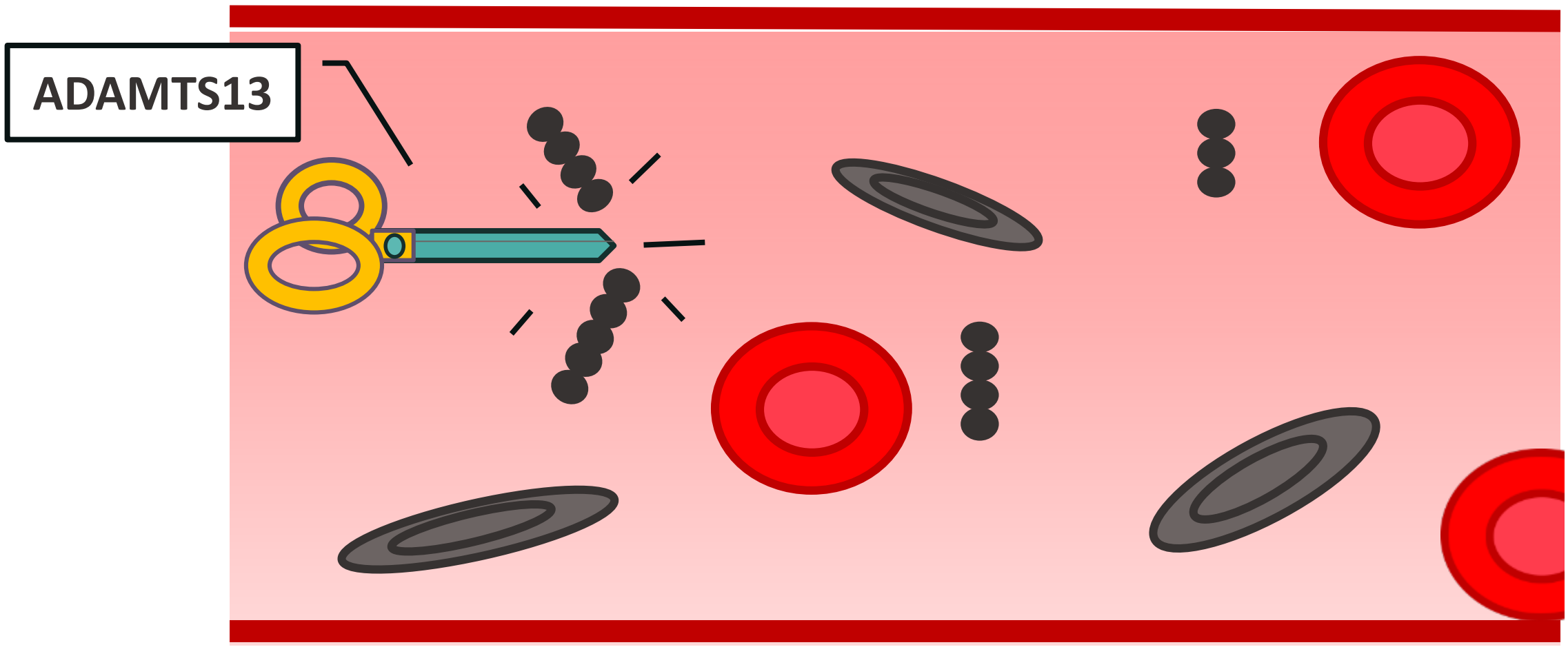

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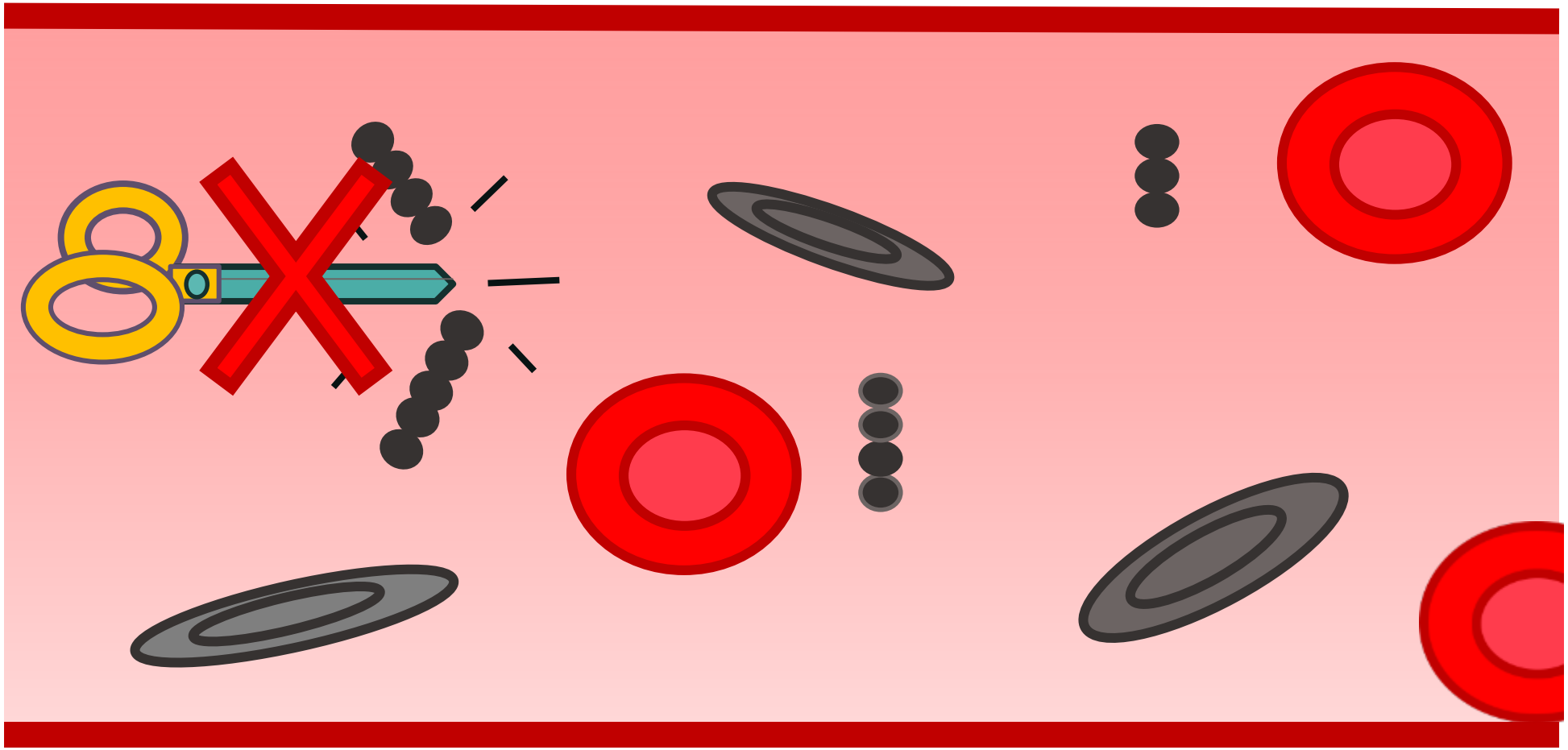

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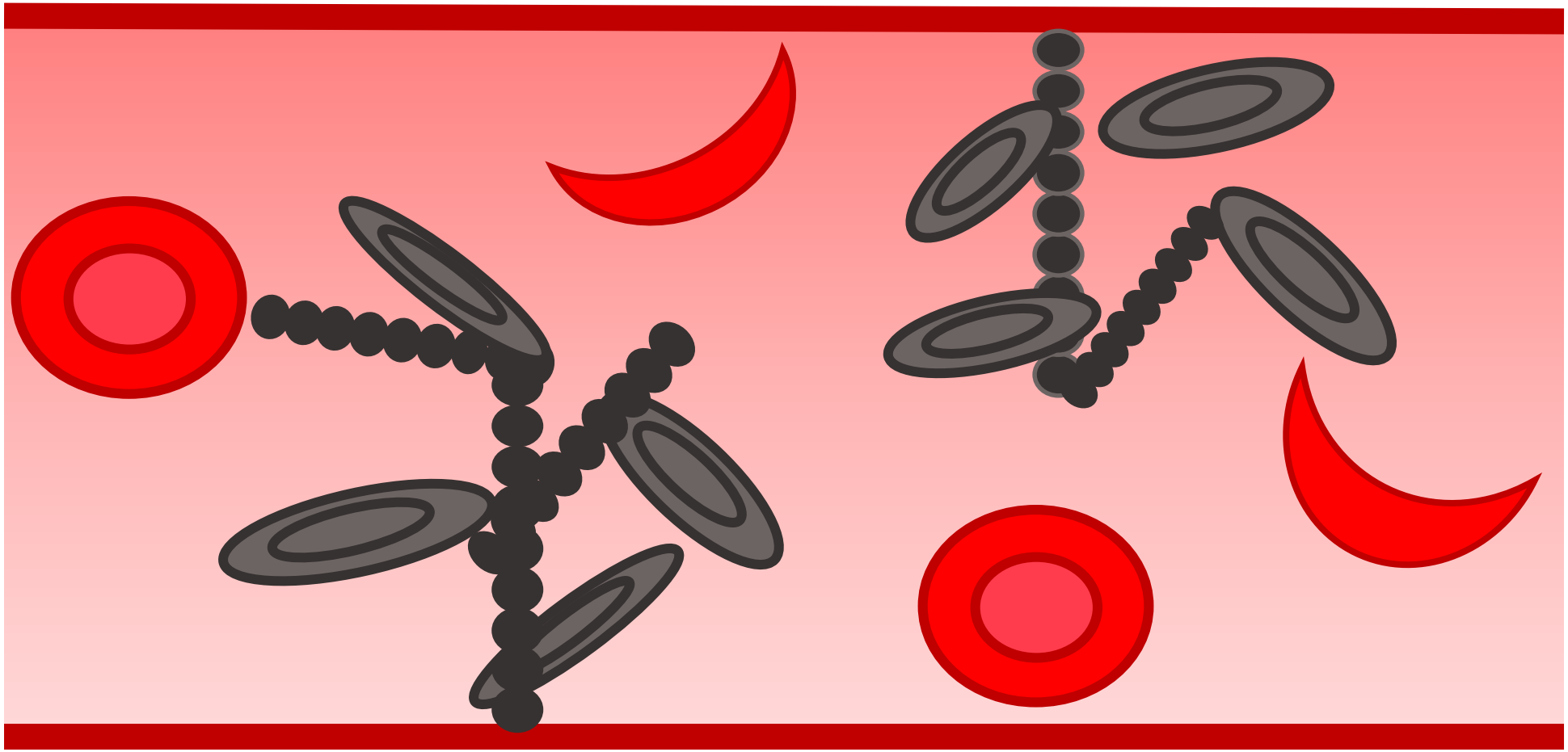

Shearing, Thrombi, Vascular occlusion

TTP: *Management*

- Thrombocytopenia
- Hemolytic Anemia
- PLASMIC score
- ADAMTS13 <10%* (send prior to PLEX)

George et al *Blood*. 2010;116(20):4060-4069

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- Hemolytic Anemia
- **PLASMIC score**
- ADAMTS13 <10%* (send prior to PLEX)

George et al *Blood*. 2010;116(20):4060-4069

TTP: *Management*

Diagnosis → Treatment → Follow-up

	Yes	No
Platelet Count <30k/uL	+1	0
Hemolysis	+1	0
Active Cancer	0	+1
MCV <90 fL	1+	0
INR <1.5	1+	0
Cr <2.0 mg/dL	1+	0

Bendapudi PK etl al . *Lancet Haematol*. 2017; Li et al. *J Thromb Haemost*. 2018;16(1):164-169.

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Total Score	Risk of ADAMTS13 <10%
Low (0-4)	0%
Intermediate (5)	6%
High (6-7)	72%

Bendapudi PK etl al . *Lancet Haematol*. 2017; Li et al. *J Thromb Haemost*. 2018;16(1):164-169.

TTP: *Management*

Diagnosis → **Treatment** → Follow-up

- Plasma exchange
- Steroids (1 mg/kg prednisone for standard risk)
- Rituximab
- +/- Caplacizumab

Zeng et al. JTH 2020

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RECOMMENDATIONS AND GUIDELINES | Free Access

ISTH Guidelines for Treatment of Thrombotic Thrombocytopenic Purpura

X. Long Zheng ✉, Sara K. Vesely, Spero R. Cataland, Paul Coppo, Brian Geldziler, Alfonso Iorio, Masanori Matsumoto, Reem A. Mustafa, Menaka Pai, Gail Rock, Lene Russell ... **See all authors**

Zeng et al. JTH 2020

TTP: *Management*

- **Plasma exchange (PLEX)**
  - 1 – 1.5 Plasma volume daily
  - Replace with FFP
  - Adverse events w/ PLEX:
    - Transfusion Reactions
    - Citrate-induced Hypocalcemia
    - Hypotensive reaction with ACE-inhibitors (discontinue)
    - Catheter-related complications

Mokrzyck et al. Am J Kidney Dis. 1994;23(6):81

TTP: *Management*

Diagnosis → **Treatment** → Follow-up

- Plasma exchange
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- **Rituximab**
- +/- Caplacizumab

Zeng et al. JTH 2020

TTP: *Management*

- **Rituximab**
  - Weekly 375 mg/m2 x 4 (administered after PLEX session)
  - Initially used for refractory TTP, now with benefit shown when used up-front
    - Decrease time to recovery*
    - Reduced exacerbation and relapse rates*

*Based on retrospective/prospective cohort studies (see Dane et al. for review TTP 2019: STATE OF THE ART)

Scully et al. Blood. 2011;118(7):1746; Page et al Blood 2016; 127(24):3092

TTP: *Management*

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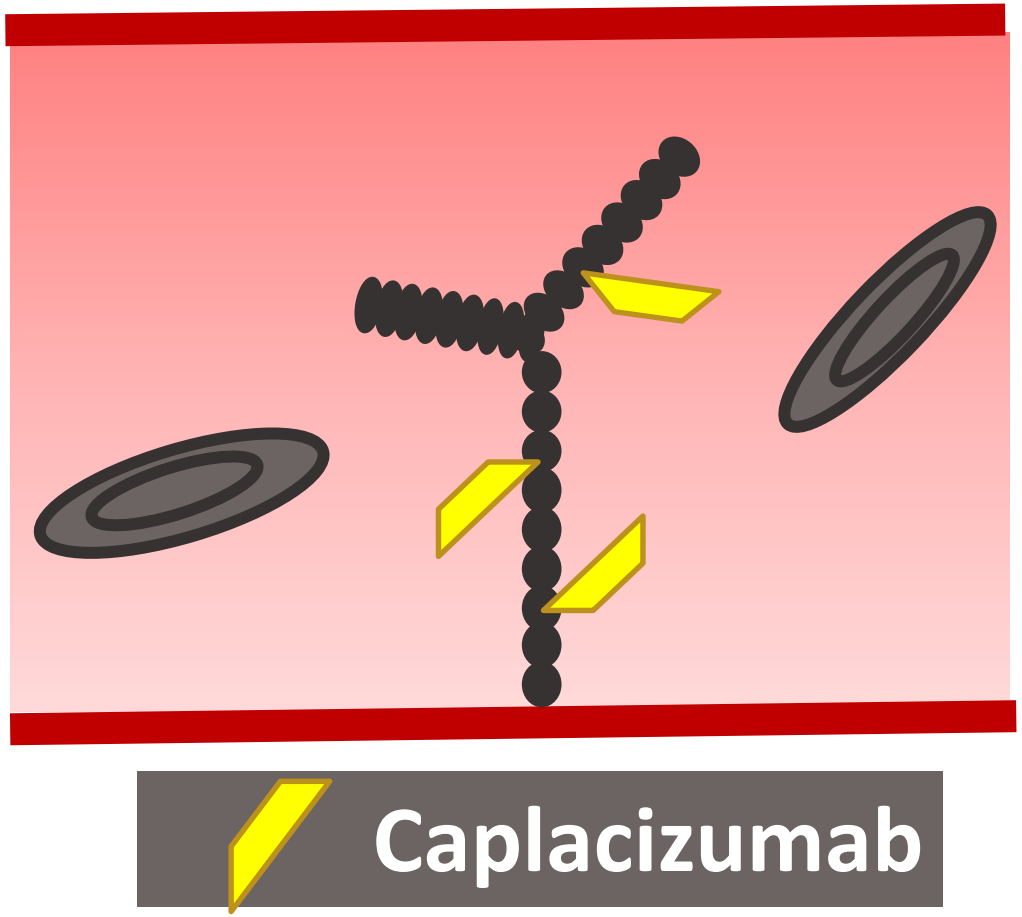
Zeng et al. JTH 2020

TTP: *Management*

Diagnosis → **Treatment** → Follow-up

- **Caplacizimumab**
  - Nanobody blocks platelet binding to vWF
  - TITAN & Hercules Trials
    - Reduced time to normalization of platelet count
    - Decreased # of PLEX sessions
    - Reduced Relapse Rate
  - Risks: Bleeding complications



Peyvandi et al. N Engl J Med 2016; 374:511-522
Scully et al. N Engl J Med 2019; 2019; 380:335-346

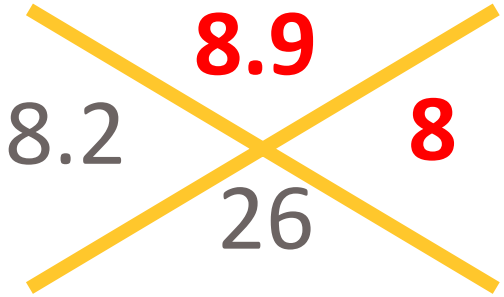
TTP: *Management*

- **Approx 40%** of acquired TTP will relapse
- Consider rituximab if ADAMTS13 <20% to prevent relapse
- Long-term complications:
  - Increased risk of pre-eclampsia
  - Stroke
  - Hypertension
  - PTSD/depression

Page et al. Blood. 2016;127(24):3092
Deford et al. Blood. 2013 Sep;122(12):2023-9
Upreti et al. *Blood* (2019) 134 (13): 1037–1045.

Case #2

23 yo F with presents with dyspnea, fatigue and petechiae……



LDH 865

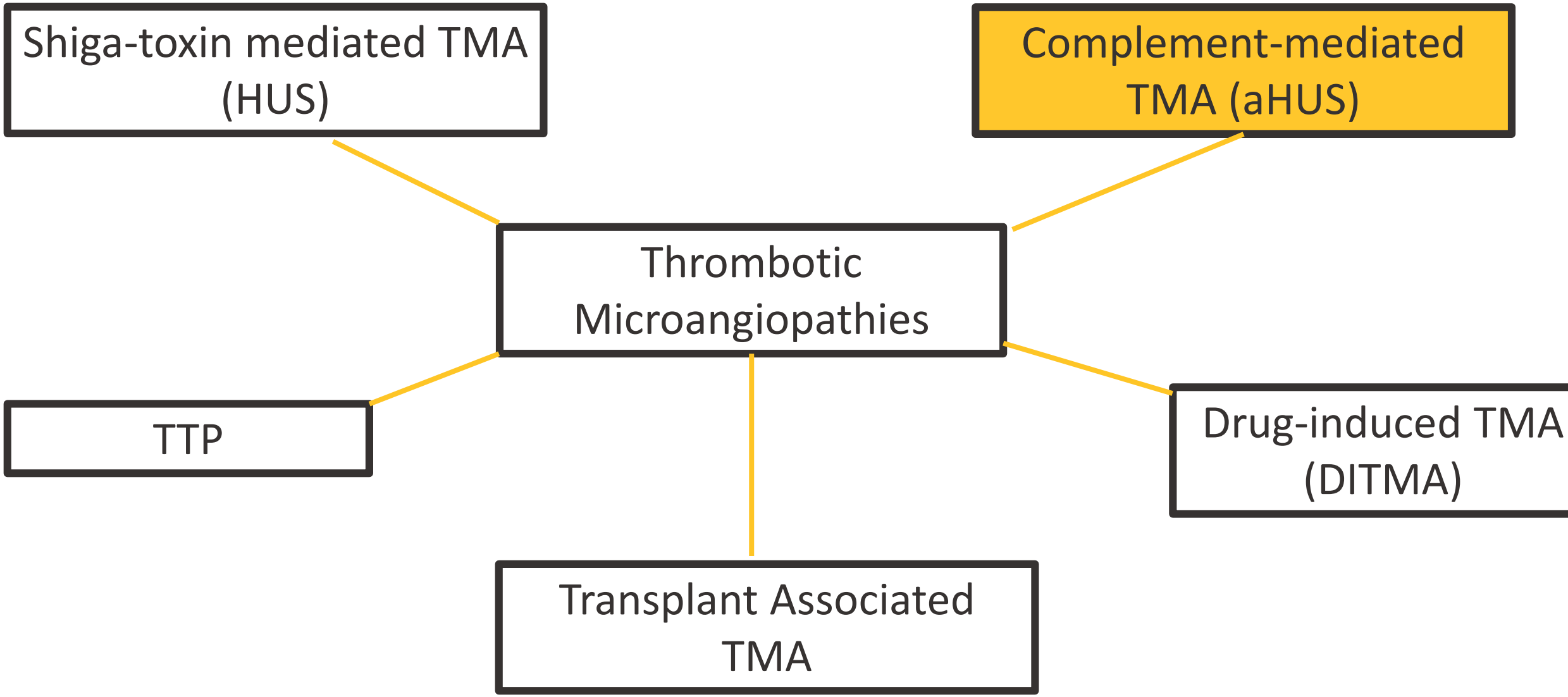
Haptoglobin <30

137	107	15
3.8	22	3.0

Started on daily PLEX and 3 days later…..

137	107	40
3.8	22	3.5

TMA-*Types*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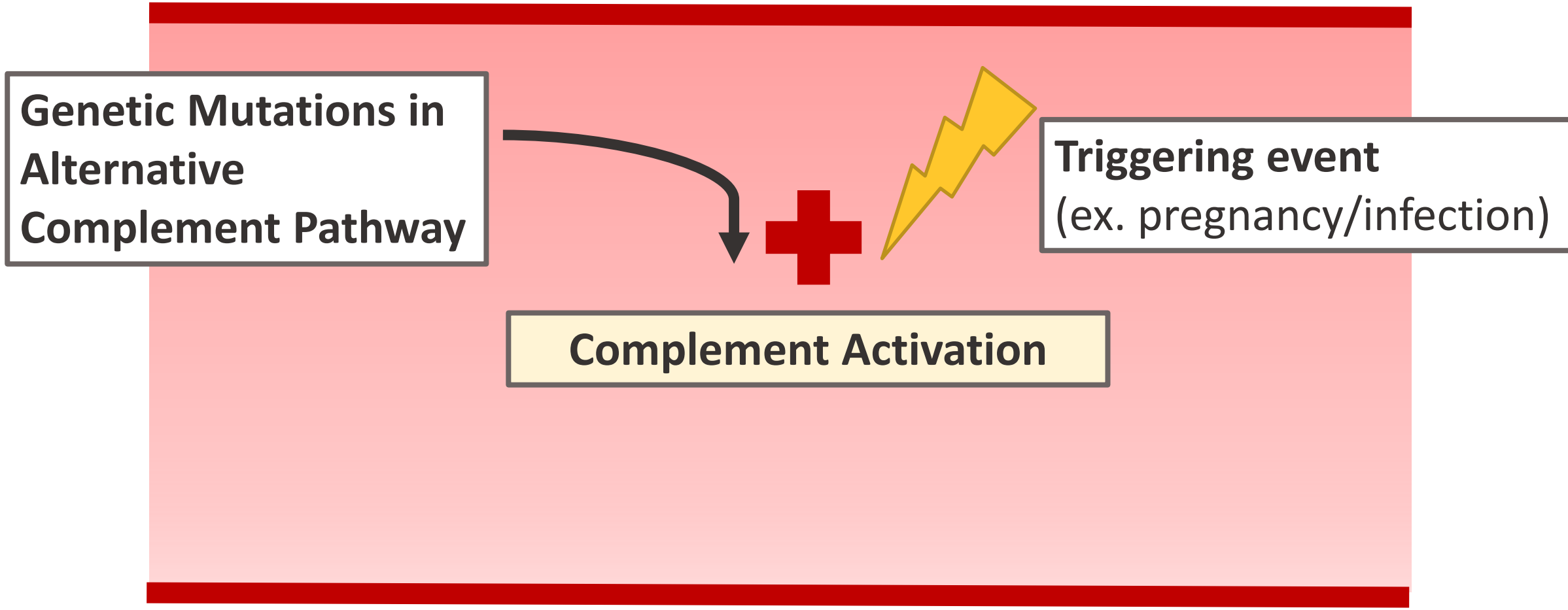
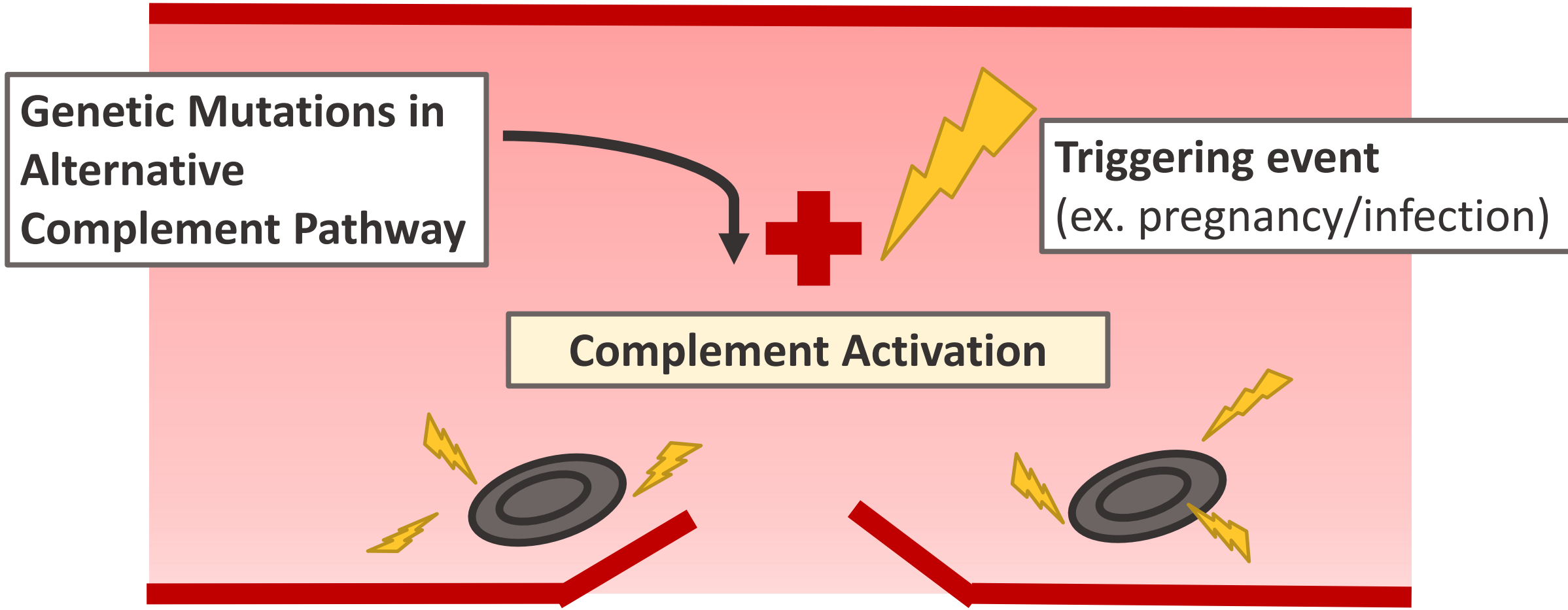
Complement-mediated TMA: *Pathogenesis*



Jokiranta. *Blood* (2017) 129 (21): 2847–2856

Complement-mediated TMA: *Pathogenesis*



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Complement-mediated TMA: *Management*

- ADAMTS13 >10%
- Lack of improvement with PLEX over 3-4 days
- Complement testing (C3,C4, CH50)
- Genetic testing + inhibitory antibodies (specialized centers- Versitas and Cinicinati Children's Hospital

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Jokiranta. *Blood* (2017) 129 (21): 2847–2856

Complement-mediated TMA: *Management*

- **Genetic testing + inhibitory antibodies**
  - Loss of function mutation in CHB, CFI, CD46
  - Gain of function mutation in CFB or C3
  - Complement factor H auto-antibody

Noris et al. N Engl J Med 2009;361:1676-87

Complement-mediated TMA: *Management*

- **Eculizumab**
  - Complement blockade
    - C5-monoclonal antibody
  - Risks: Infectious
    - Meningicoccal Vaccination
    - + Antimicrobial prophylaxis (at least for 2 weeks if not vaccinated prior)

Noris et al. N Engl J Med 2009;361:1676-87

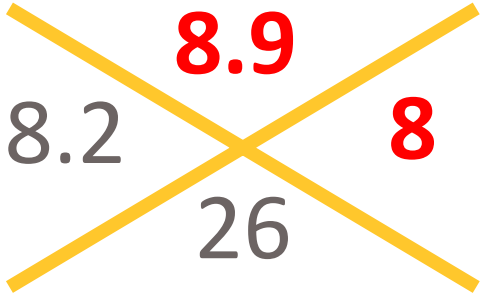
Complement-mediated TMA: *Management*

- Maintenance dosing of eculizumab every 2 weeks
- Data regarding safety of eculizumab discontinuation lacking

Jokiranta. *Blood* (2017) 129 (21): 2847–2856

Case

40 yo F with metastatic ovarian cancer receiving bevacizumab maintenance therapy presents with fatigue and petechiae.



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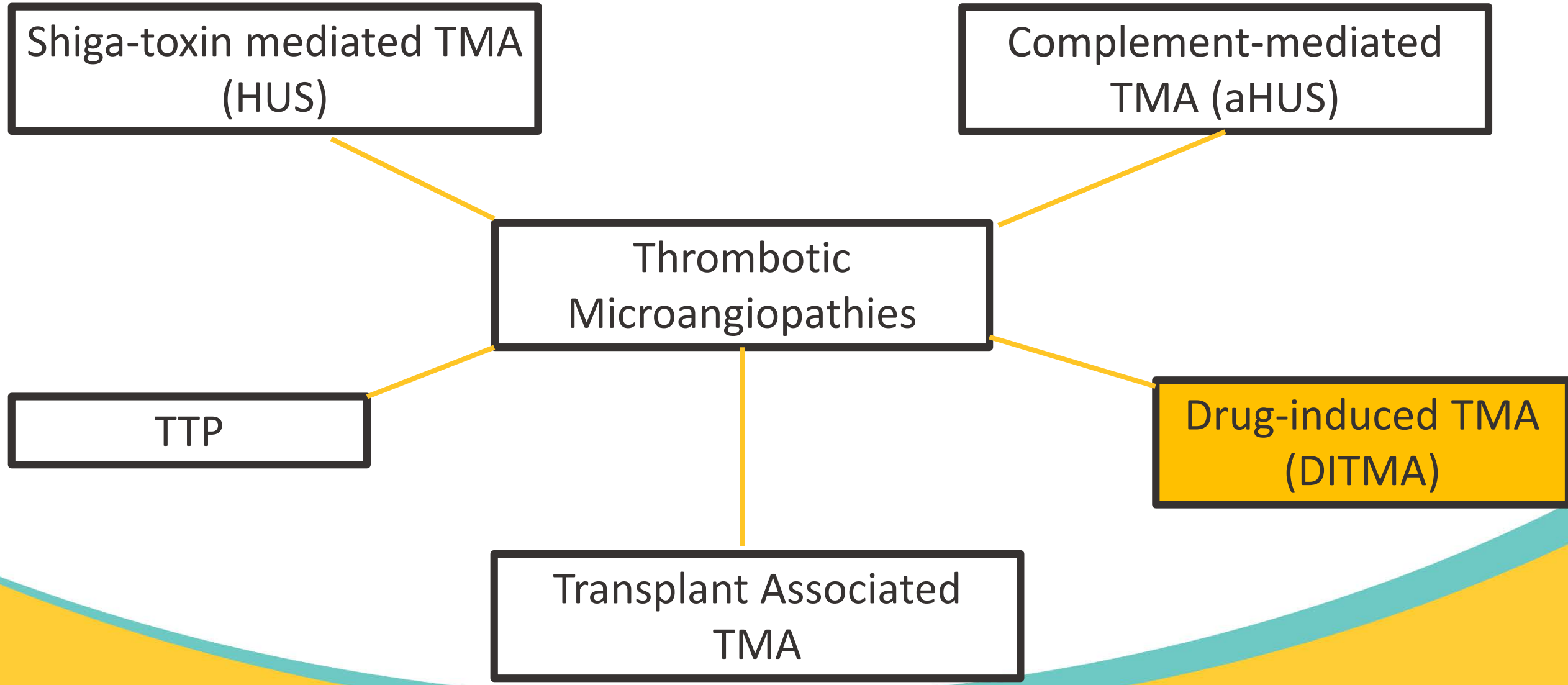
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Drug-induced TMA: *Diagnosis*

- Drugs
  - Mitomycin-C
  - VEGF
  - Gemcitabine
  - Immunosuppressive agents (tacrolimus/sirolimus/cyclosporine)
  - Emicizumab (+ FEIBA)
- Drugs of Abuse
  - Opana ER (extended release oxymorphone) administered IV

Al-Nouri et al. *Blood*. 2015;125(4):616-618

Drug-induced TMA: *Diagnosis*

- Discontinue offending agent
- Supportive Care
- Generally not responsive to PLEX

Al-Nouri et al. *Blood*. 2015;125(4):616-618

Drug-induced TMA: *Diagnosis*

- Drug Avoidance (immune cases)
- Non-immune causes
  - Decreased doses (ex. supratherapeutic cyclosporine levels)

Al-Nouri et al. *Blood*. 2015;125(4):616-618

Review of Key Points

- Differential for TMA
  - TTP, complement-mediated, transplant/drug-effect
- ADAMTS13 useful for distinguishing etiology, but not readily available
  - Clues to alternate diagnosis: Lack of responsive PLEX/severe kidney injury
- Developing Role of Novel Therapies for TTP
- Risks of eculizumab therapy & prevention
- Recognize drug-associated TMA

Thank you

Questions:

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