Microangiopatia trombotica dopo trapianto di cellule staminali ematopoietiche

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- Potentially severe complication HSCT related
- Incidence 10-35%
- More common after allogeneic HSCT
- Multi-system disease
- Kidney most commonly affected but also lung, bowel, heart and brain
- Long-term morbidity
- Some common features with TTP and aHUS

Table 4: Pathophysiologic classification of primary and secondary thrombotic microangiopathies.

Immune Mediated	**Non Immune Mediated**
Primary • Idiopathic TTP • Atypical HUS secondary to inhibitory antibodies to complement – regulating proteins	Primary • Hereditary TTP • Hereditary atypical HUS secondary to mutations in complement – regulating proteins
Secondary • Pregnancy • Autoimmune disorders • Infections • Medications (clopidogrel, ticlopidine)	Secondary • Malignant hypertension • Solid organ transplantation • HCT • Metastatic tumors • Medications (cyclosporine, tacrolimus, IFN-α, Mitomycin C)

Medit J Hemat Infect Dis 2010; 2(3)

Clinical features

- Microangiopathic hemolytic anemia
- Increased LDH
- Schistocytosis
- Hypertension

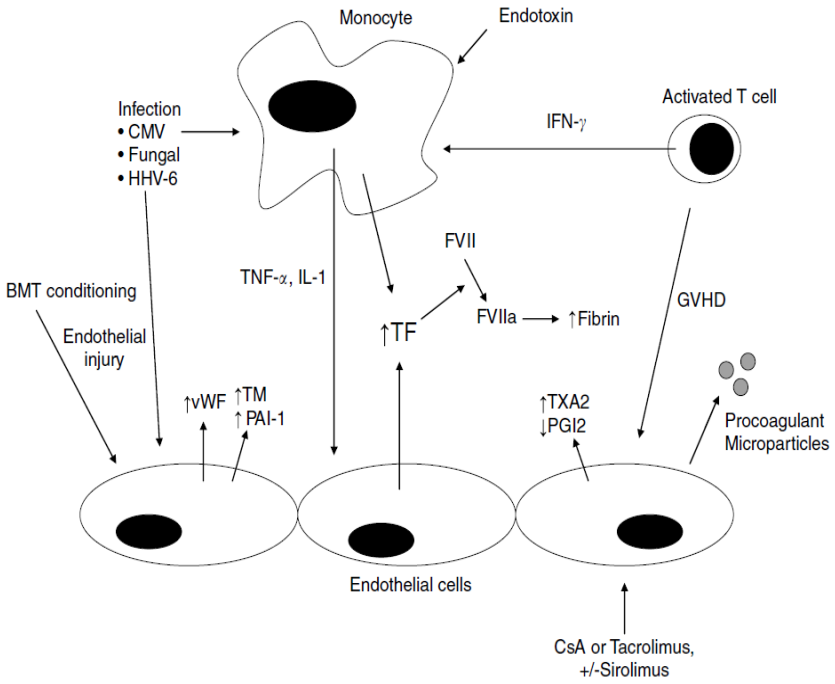
- DD: GVHD, infections, drug-induced hypertension

Risk factors

- Non modifiable: female, Afro-american race, older age
- High dose chemotherapy (busulfan, fludarabine, cisplatin)
- TBI
- Calcineurin inhibitors
- Infections (CMV, adenovirus, HHV-6, BK virus)
- GVHD

Pathophysiology

- "Final common pathway" of **endothelial damage**



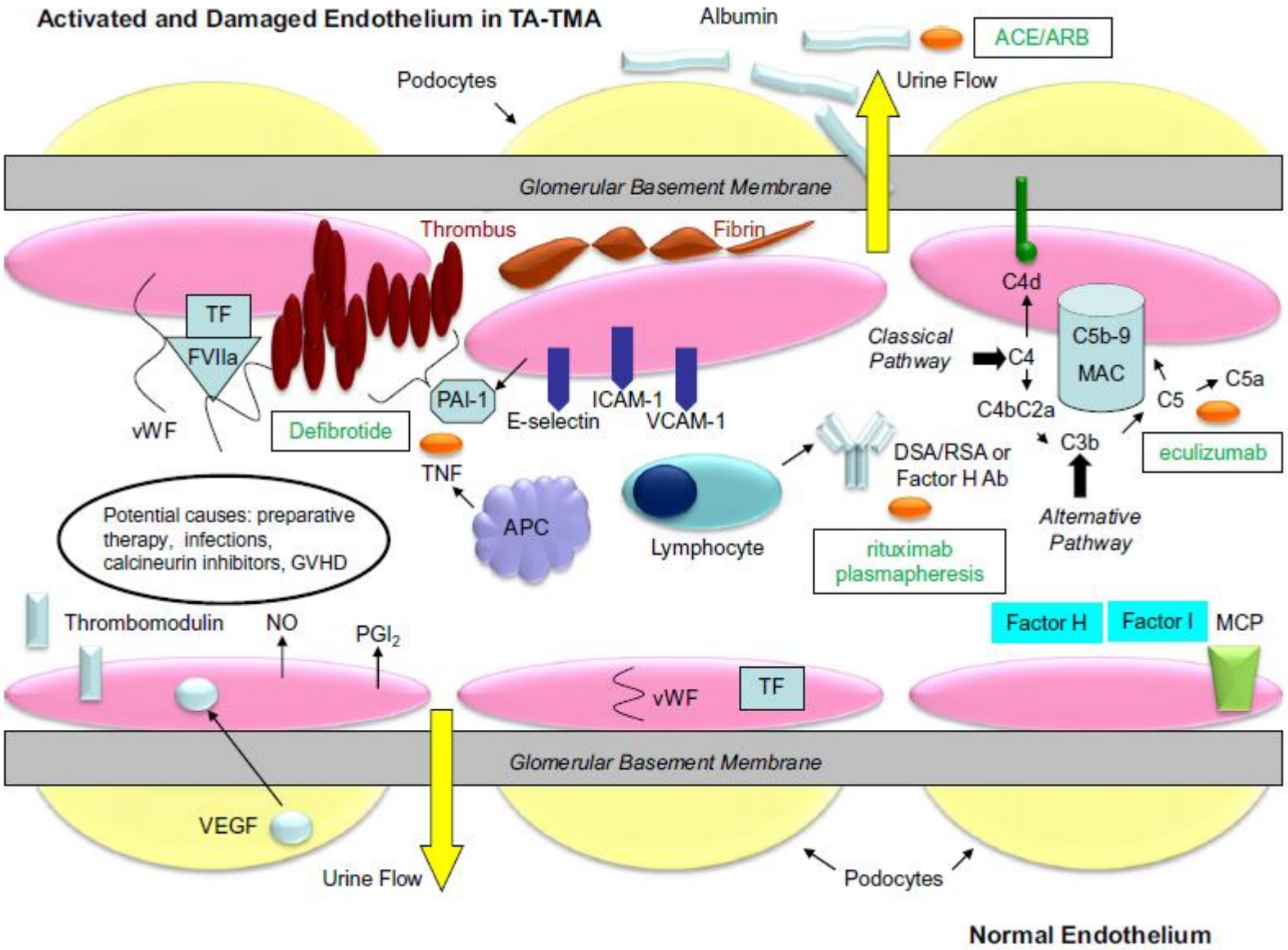
- Conditioning chemotherapy
  - busulfan, fludarabine, TBI
- Infection
  - *Aspergillus*, CMV, adenovirus, BK
- GVHD prophylaxis
  - calcineurin inhibitors (CsA, FK506)
  - rapamycin inhibitors (sirolimus)
- GVHD and Cytokines
  - produced by donor T cells
  - make endothelial cells susceptible

Bone Marrow Transplantation 2007;40:709-19.

Endothelial injury

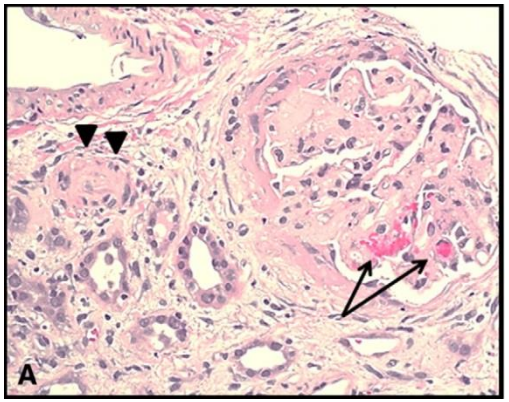
- Normal ADAMTS13 activity
- Increased vWF and thrombomodulin levels
- Circulating endothelial cells
- Complement system dysregulation:
  - CFH Abs
  - C4d deposition in glomerular capillaries
  - Haploinsufficiency of CFHR1

Evi &Hillard MJHID 2010; 2
Laskin et al, Blood 2011; 118
Jodele et al. Blood Reviews 2015



S. Jodele et al. / Blood Reviews 29 (2015) 191–204

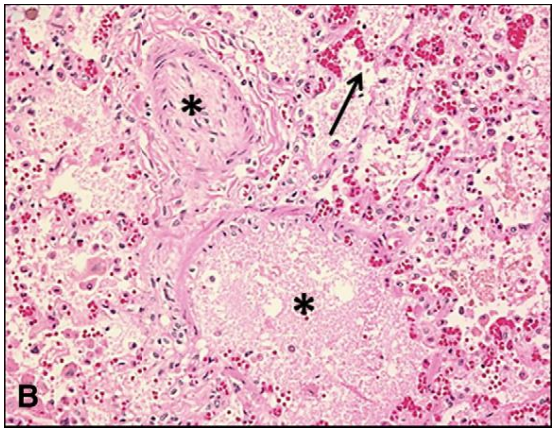
Kidney



Glomerular filtration rate reduction
Proteinuria
Hypertension

Renal biopsy: microtrombi in the glomeruli and C4d deposition in the renal arterioles

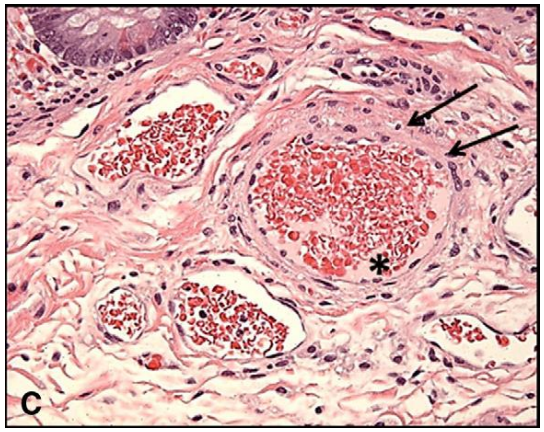
Lungs



Respiratory distress
Hypoxiemia
Pulmonary hypertension

Injured endothelium, microthrombosis and schistocyte extravasation into the lung interstitium

Gastrointestinal tract



Clinical signs:

- Severe abdominal pain
- GI bleeding
- Ileus

Radiological signs:

- Signs of ileus
- Thick mucosal wall

GI endoscopy:

- Mucosal erosions
- Mucosal hemorrhages

Histologic signs:

- Crypt loss/mucosal infarcts
- Mucosal hemorrhages/red cell extravasation
- Schistocytes and fibrinoid debris in the vessel lumen
- Endothelial cells swelling
- Total denudation of mucosa

Intestinal TMA a clinical imitator of acute GVHD

- Intestinal tract is also a target organ for TMA.

Bone Marrow Transplantation (2009) 44, 43–49

www.nature.com/bmt

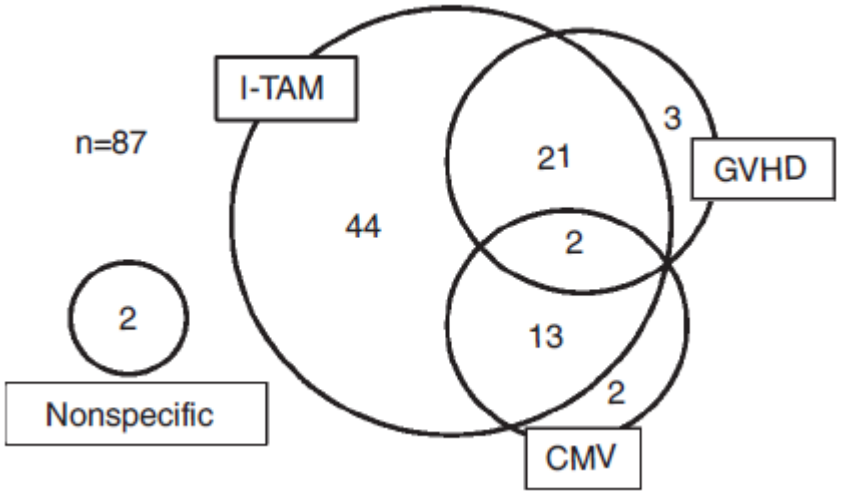
ORIGINAL ARTICLE

Clinicopathological manifestations and treatment of intestinal transplant-associated microangiopathy

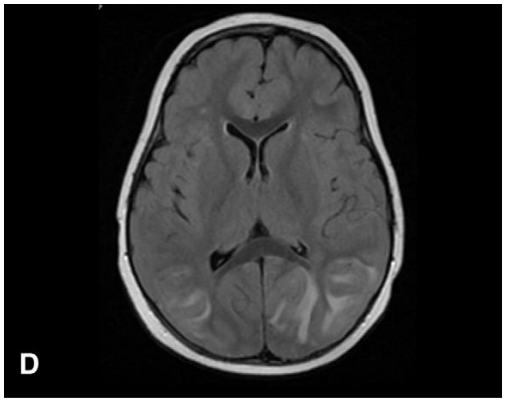
- Allo-SCT
- Severe diarrhea (>1000mL/day)
- Abdominal pain

↓ Colonscopic Bx

- TMA: 92% of the patients with severe diarrhea after allo-HSCT
- Coexistent with GVHD in 30%



Central nervous system



Confusion
Headaches
Hallucination
Seizures

Acute uncontrolled TMA-associated hypertension

Most common TA-TMA-related CNS injury

Polysierositis

- Pericardial effusion: 45% incidence in TA-TMA (Lerner et al, 2014)
- Pleural effusion
- Ascites

DD: cGVHD

Diagnostic criteria

BMT CTN Toxicity Committee Consensus Definition for TMA
RBC fragmentation and >2 schistocytes per high-power field on peripheral smear
Concurrent increased serum LDH above institutional baseline
Concurrent renal* and/or neurologic dysfunction without other explanations
Negative direct and indirect Coombs test results

**Doubling of serum creatinine from baseline (baseline creatinine before hydration and conditioning) or 50% decrease in creatinine clearance from baseline.*

Diagnosis

Blood 2011;118:1452-62.

Table 1. Current diagnostic guidelines for TA-TMA

Category	Blood and Marrow Transplant Clinical Trials Network[18]	International Working Group of the European Group for Blood and Marrow Transplantation[58]	Probable TMA as defined by validation study by Cho et al[53]
Schistocytes	≥ 2 per high-power field in peripheral blood	> 4% in peripheral blood	≥ 2 per high-power field in peripheral blood
LDH	Increased above institutional baseline	Sudden and persistent increase	Increased
Renal function	Doubling of serum creatinine or 50% decrease in creatinine clearance from baseline before transplantation		
Platelets		Thrombocytopenia: $< 50 \times 10^9$/L or a ≥ 50% decrease in platelet count	Thrombocytopenia: $< 50 \times 10^9$/L or a ≥ 50% decrease in platelet count
Red cells		Decreased hemoglobin or increased red blood cell transfusions	Decreased hemoglobin
CNS	Unexplained neurologic dysfunction		
Coombs test	Negative direct and indirect		Negative
Haptoglobin		Decreased	Decreased
Other			No coagulopathy

Causes of late diagnosis

- Anemia, thrombocytopenia is relatively common in SCT recipients.
- Renal dysfunction, CNS symptoms were present in only 20%.

Transplantation 2006;82:638-44.

- <15% of patients with biopsy-proven TA-TMA fulfilled clinical criteria.

Bone marrow transplant 2009;44:43-9.

Diagnostic criteria for TA-TMA.

The diagnosis of TA-TMA maybe be established	
A. Microangiopathy diagnosed on tissue biopsy or B. Laboratory and clinical markers indicating TMA	
Laboratory or clinical marker	Description
[1]Lactate dehydrogenase (LDH)	Elevated above the upper limit of normal for age
[2]Proteinuria	A random urinalysis protein concentration of ≥30 mg/dL
[3]Hypertension	>18 years of age: a blood pressure at the 95th percentile value for age, sex and height. ≥18 years of age: a blood pressure ≥140/90 mm Hg.
[4]De novo thrombocytopenia	Thrombocytopenia with a platelet count $<50 \times 10^9$/L or a ≥50% decrease in the platelet count
[5]De novo anemia	A hemoglobin below the lower limit of normal for age or anemia requiring transfusion support
[6]Evidence of microangiopathy	The presence of schistocytes in the peripheral blood or histologic evidence of microangiopathy on a tissue specimen
[7]Terminal complement activation	Elevated plasma concentration of sC5b-9 above upper normal laboratory limit

[1,2,3]Present: consider diagnosis of TA-TMA. Monitor very closely.
[2 + 7] at TA-TMA diagnosis indicate high features associated with poor outcome: consider therapeutic intervention.

Jodele et al. Blood Reviews 2015

Treatment

- Withdrawal or minimization of potential triggering agents (cyclosporine, tacrolimus, sirolimus) with caution
- Replacement with alternative immunosuppressive medications (corticosteroids, mycophenolate mofetil, azathioprine and methotrexate)
- Treatment of co-existing conditions (infections and GVHD) that may promote TA-TMA.
- Aggressive hypertension management

Manipulation of GVHD Prophylaxis

ORIGINAL ARTICLE

Intestinal thrombotic microangiopathy induced by FK506 in rats

M Fujino[1], Y Kim[2,3] and M Ito[1,2]

[1]*Department of Pathology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan;* [2]*Department of Pathology, Nagoya University Hospital, Nagoya, Japan and* [3]*Department of Clinical Pathology, St Mary's Hospital, Catholic University, Seoul, Korea*

- The extent of TMA was proportional to the FK506 blood levels.
- Recovered from TMA after withdrawal of FK506 injection.
- Decreased VEGF, PGI2 or NO, direct cytotoxic damage could be possible mechanisms.

Bone marrow transplant 2007;39:367-72.

- Replacing calcineurin inhibitors with other immunosuppressive agents may be beneficial. (ex. Mycophenolate mofetil)

Therapeutic plasma exchange

Table 2. Summary of recent studies (2003-present) assessing outcomes of therapeutic plasma exchange in TA-TMA

Author, year of publication	Patients receiving TPE/total patients with TA-TMA (n/n)	Response to TPE, %	Mortality, %	Additional findings and author conclusions
Hahn et al, 2004[73]	19/19		84	
Uderzo et al, 2006[19]	17/64	59	50 for all	Outcome influenced by defibrotide
Erdbruegger et al, 2006[43]	5/5	40	20	
Worel et al, 2007[16]	11/11	64		Treated prospectively with withdrawal of cyclosporine and TPE at TA-TMA diagnosis
Oran et al, 2007[72]	63/66	64	100 for nonresponders 50 for responders	Response was related to GVHD and infection control
Cho et al, 2008[38]	16/43		62 for all	TA-TMA should be treated early before it develops into definite tissue injury
P-TMA	5/27	80	48	
D-TMA	11/16	27	92	
Willems et al, 2010[17]	25/42	55 for all	80 for all	Median survival in responders 218 days versus 27 days in nonresponders

Median response rate 59% (27%-80%)

Blood 2011;118:1452-62.

Worel et al Prospective study RR 64% in pts treated with immediate withdrawal of Ciclosporine and initiation of TPE

Transfus Apher Sci 2007; 36: 297-304

Therapeutic plasma exchange

TABLE 2. TA-TMA features and response to therapy*

Patients	Survived (n = 5)	Died (n = 5)	p value
Day after HSCT of TA-TMA diagnosis	35 (28, 36) (9-41)	47 (26, 92) (25-240)	0.35
Maximum fold elevation of pre-BMT creatinine	10.2 (1.6, 10.3) (1.5-13.0)	4.8 (3.6, 5.4) (2.0-16.6)	0.92
Urine protein/creatinine ratio	13.0 (2.4, 13.0) (2.4-13.0)[22]	20.0 (5.0, 95.5) (2.0-159.0)[22]	0.72
Rituximab doses	5 (4, 7) (4-7)	10 (9, 16) (4-17)	0.07
Days to initiation of TPE after TA-TMA diagnosis	17 (5, 25) (4-25)	32 (17, 57) (17-73)	0.11
Number of TPE sessions to resolution of microangiopathy	25 (23, 26) (17-32)	69 (42, 75) (38-79)	0.01
Resolution of microangiopathy	5/5	4/5	1.00
Number of days to resolve microangiopathy after starting TPE	14 (14, 15) (10-16)	54 (38, 67) (32-70); n = 4	0.004†
Complete resolution of TA-TMA	5/5	0/5	0.01
Number of RRT sessions to resolution of renal failure	19 (7, 30) (7-30); n = 3	98 (64, 154) (43-199); n = 4	0.03†
Number of days for creatinine to return to pre-HSCT baseline after starting TPE	40 (32, 54) (15-127)	Never normal until death	0.004‡
Recovery of renal function by nucGFR (mL/min/1.73 m^2)	95 (68, 148) (65-171); n = 4	None of patients recovered from ESRD	NA

Early initiation of plasma exchange might be beneficial even in patients with multiorgan failure due to TA-TMA.

Jodele el al. Transfusion. 2013

Apply early in TAM
Daily for extended period of time
In combination with other agents (rituximab, defibrotide)

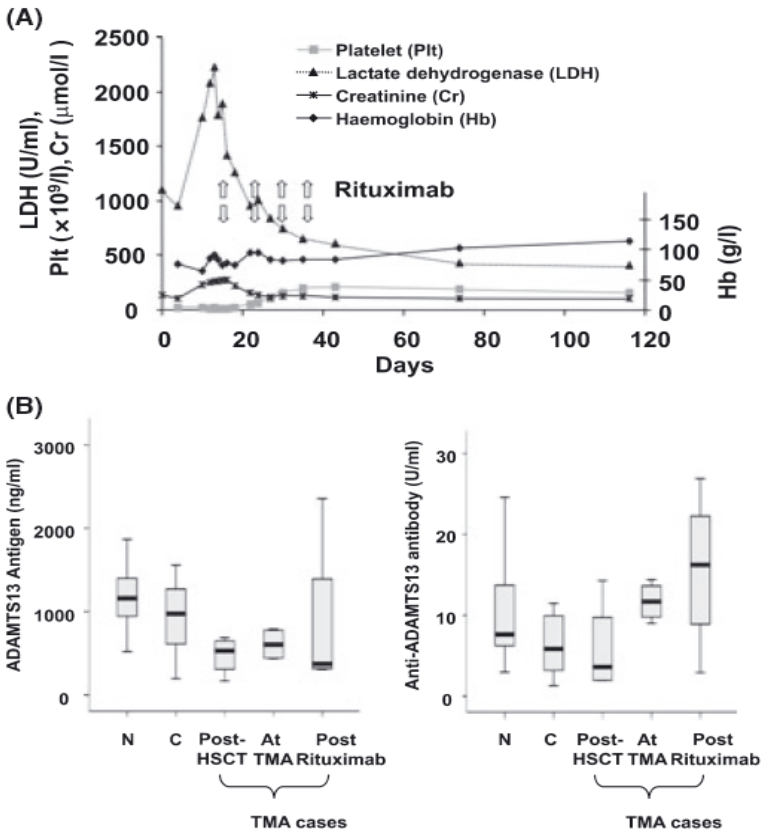
Jodele et al. Blood Reviews 2015

Potential therapies

Agent	*Number treated*	*Treatment*	*Response*	*Overall survival*	*References*	*Comment*
Daclizumab	13	Daclizumab 1 mg/kg 4 weekly (2 mg/kg loading dose); discontinuation of calcineurin inhibitor and sirolimus	Five CR, two PR	4/13	[95]	Treatment started after diagnosis of TMA; most deaths due to infection
Defibrotide	12	Defibrotide 40 mg/kg orally per day	Five CR, three PR	6/12	[96]	Treatment started after diagnosis of TMA; no deaths attributable to TMA
Rituximab	5	Rituximab 375 mg/m^2/ week × 4 doses	Four CR	3/5	[97]	All patients failed at least 7 days plasma exchange and high-dose cortico-steroids before rituximab
EPA	7	EPA 1.8 g orally per day	N/A	7/7	[98]	Treatment started 3 weeks before transplant; no TMA in treated group, TMA developed in 4 of 9 untreated patients
Transdermal isosorbide	1	Transdermal isosorbide tape 20 mg daily	1	1/1	[99]	No side effects observed

Bone Marrow Transplantation 2007;40:709-19.

Rituximab



Alone or in association with defibrotide

Anticorpal depletion and immune regulation

5 pts treated unresponsive to TPE and PDN

375mg/m^2x4

4 CR

Br J Haematol. 2007;137:475-8

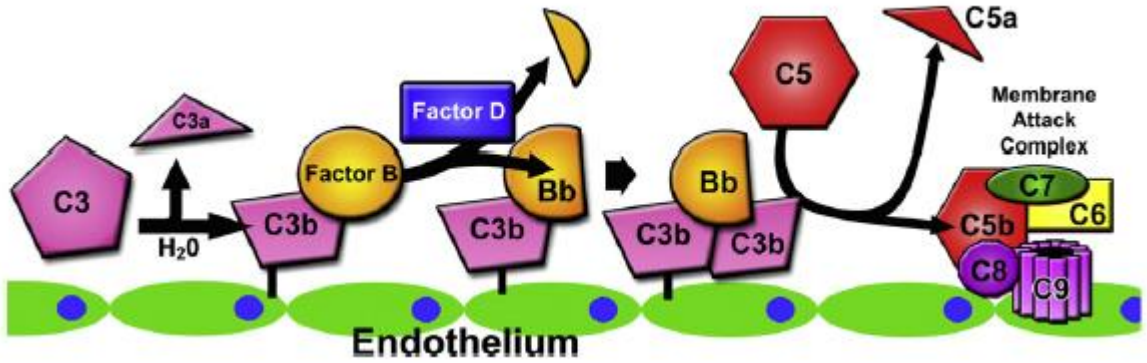
Defibrotide

- Profibrinolytic, antithrombotic, anti-inflammatory activity
- Inhibition of TNFa-mediated endothelial cells apoptosis in vitro, reducing PAI-1 activity
- CRR 30-60% in VOD
- Protective activity to the endothelium damage by cyclosporine, tacrolimus, sirolimus
- Used in monotherapy or in combination
- Two Italian multicenter retrospective studies
  - 13.8% TMA incidence
  - RR 55%
  - Same dosage used in VOD

Uderzo et al, BMT 2000; 26: 1005-9
Corti et al, BMT 2002; 29: 542-3

Eculizumab

- Monoclonal antibody directed towards C5
- Prevents formation of C5b-9 membrane complex attack
- 18 pts treated
- CRR>60%
- 4-6 weeks of induction therapy



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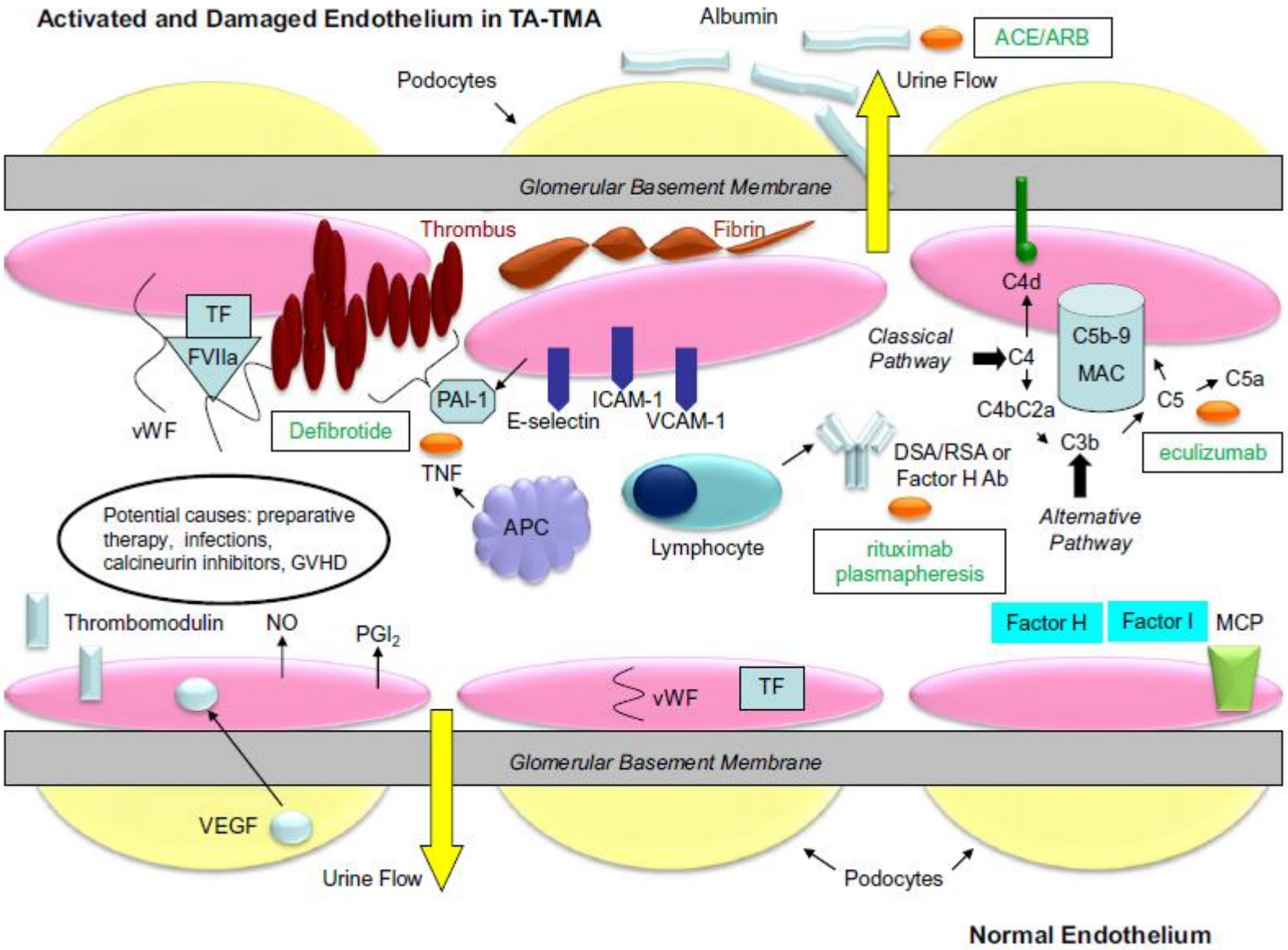

S. Jodele et al. / Blood Reviews 29 (2015) 191–204

Prognosis

- TA-TMA is a life-threatening complication of SCT.
- Kidney injury both acute and chronic is a significant complication
- Risk of needing dialysis is 8% in retrospective pediatric studies
- Kidney function 40% of normal 2 years after transplantation
- NRM in pts with TA-TMA 43.6% vs 7.8% in pts without

Jodele S et al, Blood 2014;124: 645-653
Rajpal JS et al, BBMT 2013; 19:661-5
Glezerman IG et al, BBMT 2010; 16: 976-84

Conclusions

- TA-TMA is a multi-visceral disease related to a microvascular endothelial injury.
- The kidney is most often affected but also pulmonary, gastrointestinal and CNS involvement should be considered.
- Complement dysregulation plays an important role.
- Clinical interventions should be considered early to increase success.