Vascular Endothelial Syndromes to allo-HSCT

Sergio Siragusa

PROMISE, UniPa

Vascular Endothelial Syndrome (VESs)

Early/Late allo-HSCT life-threatening complications

Group of complications without well-established origins, clinically characterized by thrombosis and/or bleeding and MOF

- Sinusoidal Obstruction Syndrome/VOD
- Capillary Leak Syndrome
- Engraftment Syndrome
- Transplant-Associated Microangiopathy (TAM)
- Diffuse Alveolar Haemorrhage (DAH)
- Idiopathic Pneumonia Syndrome

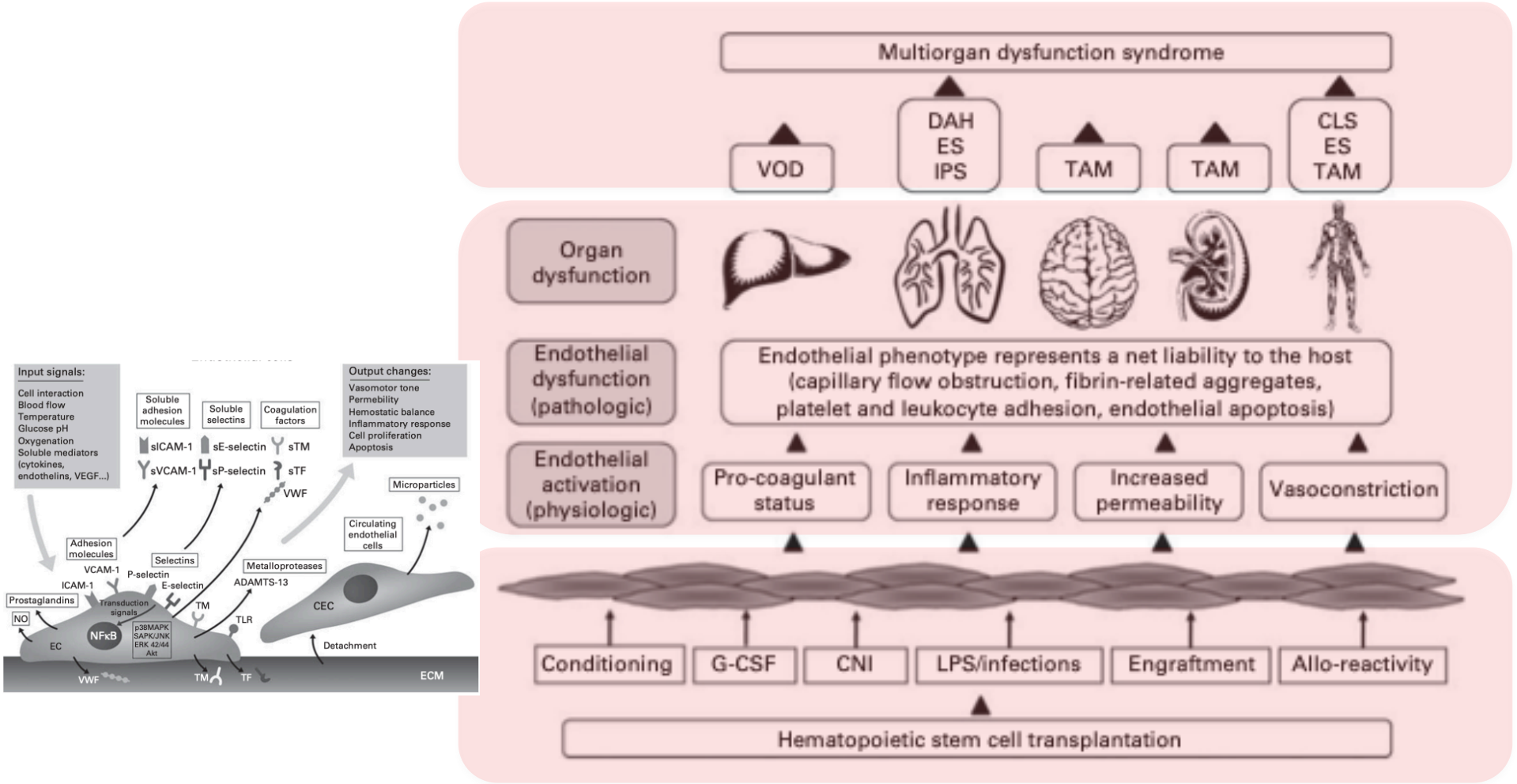
Early onset after HSCT, overlapping clinical manifestations, the absence of well-defined clinical criteria for diagnosis (and consequently an unknown true incidence), the absence of well-established treatments, and the tendency to evolve to an irreversible multiorgan dysfunction syndrome

Clinical Manifestation of VESs

Symptoms and signs	*VOD*	*CLS*	*ES*	*DAH*	*IPS*	*TAM*
Usually starting on day:	0–7	7–10	11–15	11–19	18–23	25–120
Fever		✓	✓		✓	✓
Jaundice	✓					
Hepatomegaly	✓					
Weight gain	✓	✓	✓			
Oedemas	✓	✓				
Ascites	✓	✓				
Lung infiltrates	✓	✓	✓	✓	✓	
Dyspnoea	✓	✓	✓	✓	✓	
Hypoxia	✓	✓	✓	✓	✓	
Diarrhoea			✓			
Renal dysfunction	✓	✓	✓			✓
Neurological dysfunction			✓			✓
Evolution to MODS	✓	✓	✓		✓	✓
Predominant in:	allo	auto	auto	allo	allo	allo

Carreras E et al. Bone Marrow Transplantation (2011) 46, 1495–1502

Pathogenesis of VESs after HSCT



Carreras E et al. Bone Marrow Transplantation (2011) 46, 1495–1502

Early/Late allo-HSCT life-threatening complications

Group of complications without well-established origins, clically characterized by thrombosis and/or bleeding and MOF

- **Sinusoidal Obstruction Syndrome/VOD**
- Capillary Leak Syndrome
- Engraftment Syndrome
- **Transplant-Associated Microangiopathy (TAM)**
- Diffuse Alveolar Haemorrhage (DAH)
- Idiopathic Pneumonia Syndrome

Early onset after HSCT, overlapping clinical manifestations, the absence of well-defined clinical criteria for diagnosis (and consequently an unknown true incidence), the absence of well-established treatments, and the tendency to evolve to an irreversible multiorgan dysfunction syndrome

Early/Late allo-HSCT life-threatening complications

Group of complications without well-established origins, clically characterized by thrombosis and/or bleeding and MOF

- **Sinusoidal Obstruction Syndrome/VOD**
- Capillary Leak Syndrome
- Engraftment Syndrome
- **Transplant-Associated Microangiopathy (TAM)**
- Diffuse Alveolar Haemorrhage (DAH)
- Idiopathic Pneumonia Syndrome

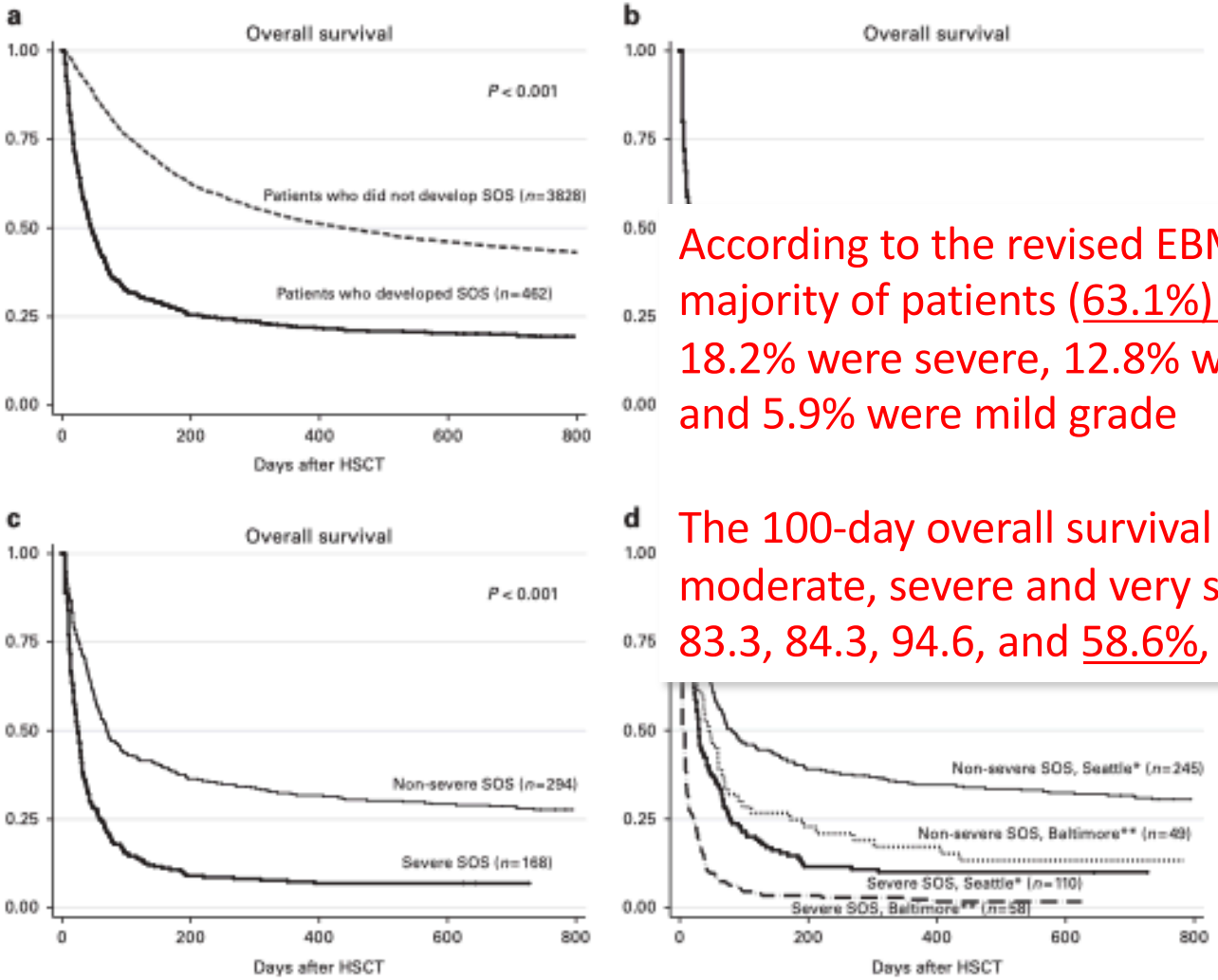
Early onset after HSCT, overlapping clinical manifestations, the absence of well-defined clinical criteria for diagnosis (and consequently an unknown true incidence), the absence of well-established treatments, and the tendency to evolve to an irreversible multiorgan dysfunction syndrome

SOS/VOD

- Sinusoidal obstruction syndrome (SOS)(Veno Occlusive Disease (VOD) is a potentially lethal complication of HSCT
- Its reported incidence ranges from 5% to over 50%. This variability in SOS incidence may result from the use of different diagnostic criteria **(actual est. 10%)**
- SOS usually occurs within the first 3 weeks after allo-HSCT as a result of endothelial and hepatic damage caused by the conditioning regimen
- Because SOS is associated with low platelet count and ascites, it is usually diagnosed by clinical manifestations rather than liver biopsy

K Yakushijin et a. Bone Marrow Transplantation (2016) 51, 403–409

Overall survival in patients with SOS following HSCT

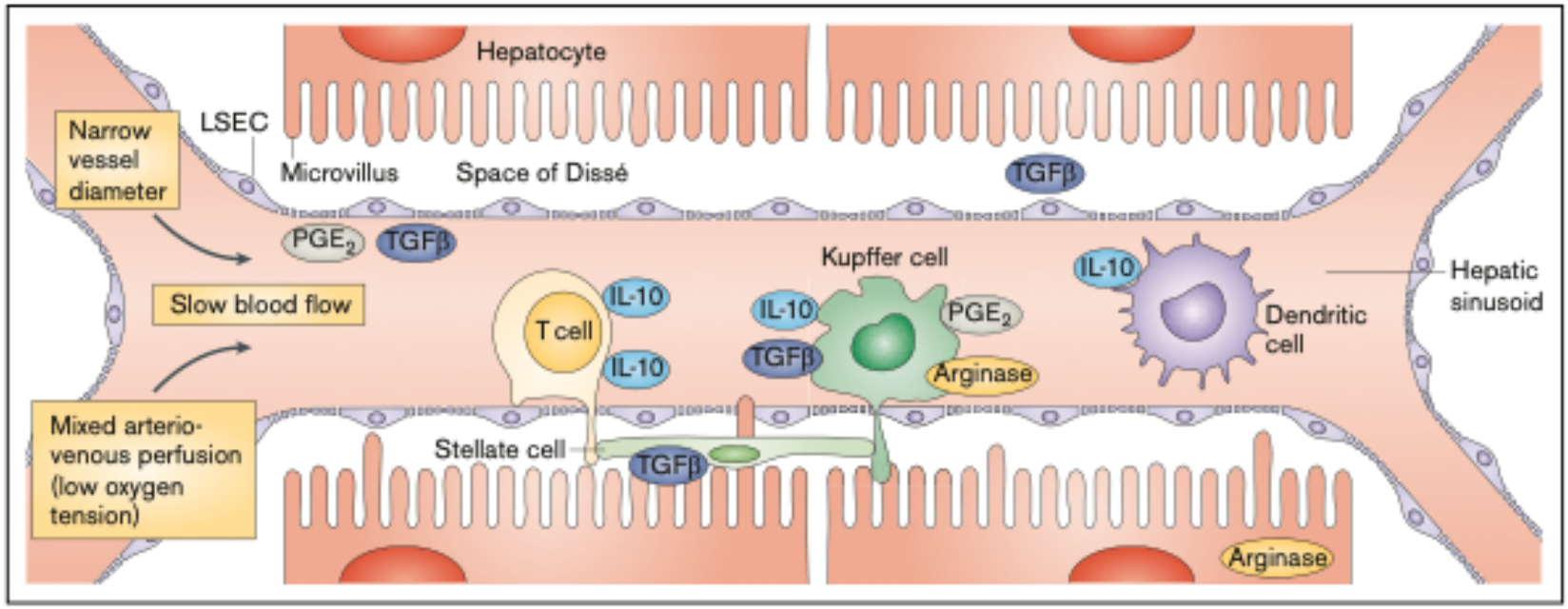


According to the revised EBMT criteria, the majority of patients (63.1%) were very severe, 18.2% were severe, 12.8% were moderate, and 5.9% were mild grade

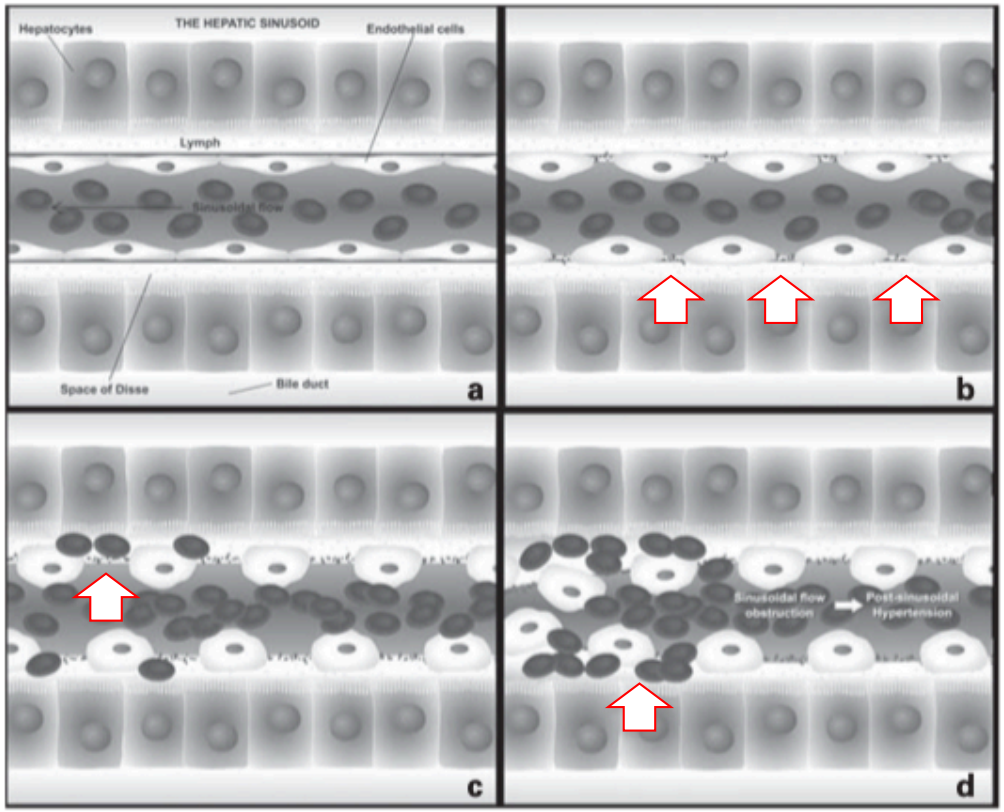
The 100-day overall survival (OS) of mild, moderate, severe and very severe groups was 83.3, 84.3, 94.6, and 58.6%, respectively

Yoon JH et a. Bone Marrow Transplant. 2019 Aug;54(8):1361-1368

Anatomy of the hepatic sinusoid



SOS/VOD pathogenesis



(1) Sinusoidal ECs damaged during conditioning round up favouring the appearance of gaps in the sinusoidal barrier;

(2) RBC begin to penetrate into the space of Disse detaching the endothelial lining;

(3) The sloughed sinusoidal lining cells embolize downstream and **obstruct the sinusoidal flow** (sinusoidal obstruction syndrome).

Carreras E et al. Bone Marrow Transplantation (2011) 46, 1495–1502

SOS/VOD rCriteria/Risk Factors

Adult Criteria	
Classical VOD/SOS (Baltimore Criteria)	Late-Onset VOD/SOS
• Onset in the first 21 days after HSCT	• Onset beyond day 21 post-HSCT
• Bilirubin ≥2 mg/dL plus 2 or more of:	• Classical VOD/SOS (Baltimore criteria)
• Painful hepatomegaly	**OR**
• Weight gain >5%	• Histologically proven VOD/SOS
• Ascites	**OR**
	• Two or more of the following:
	• Bilirubin ≥2 mg/dL (or 34 μmol/L)
	• Painful hepatomegaly
	• Weight gain >5%
	• Ascites
	AND
	• Hemodynamic and/or ultrasound evidence of VOD/SOS
Pediatric Criteria	
• No limitation for time of onset of VOD/SOS	
• Presence of ≥2 of the following*:	
• Unexplained consumptive and transfusion-refractory thrombocytopenia†	
• Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics or a weight gain >5% above baseline value	
• Hepatomegaly‡ (best if confirmed by imaging) above baseline value	
• Ascites‡ (best if confirmed by imaging) above baseline value	
• Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥2 mg/dL within 72 h	

Patient-Related Factors	OR	Transplantation-Related Factors	OR
Young age [5,24]	1.7-9.5	Allogeneic HSCT [24]	2.8
Preexisting hepatic condition		Unrelated/HLA mismatch [24]	1.4
Previous liver disease [24]	3.4		
Elevated AST/ALT pre-HCST [24]	2.4-4.6		
Hepatitis C-positive [26]	2.2		
Underlying diagnosis		Previous HSCT [24]	1.9
Leukemia [24]	2.2		
Previous treatment		High-intensity/MAC regimens	2.3-7.9
Gemtuzumab ozogamicin [24]	19.8	Busulfan plus cyclophosphamide [24]	3.9-5.1
Inotuzumab ozogamicin [6]*	22	Fludarabine [24]	4.0
		TBI-based [26]	1.73
		Busulfan-based [26,30]	2.43
		Busulfan-thiotepa [36]	8.8
Previous abdominal radiation [24]	2.9	Total body irradiation [24]	
		>12 Gy plus cyclophosphamide	2.8
Impaired pulmonary function [24]	2.4	GVHD prophylaxis [24]	
Genetic predisposition [24]		Sirolimus + methotrexate + tacrolimus	~3
GSTM1 null genotype	4.1	Methotrexate + cyclosporine	3.3
KPS score <90% [24]	2.7	Cyclosporine	4.2
Ferritin >1000 ng/mL pre-HSCT [24]	3.1	Horse ATG [37]	3.5
Ferritin ≥950 ng/mL pre-HSCT [36]	8.8		
Sepsis post-HSCT [24]	4.1	Trough serum tacrolimus levels above target range (5-10 ng/mL) [21]	NR
ECOG performance status 2-4 (vs 0-1) [26]	1.9	Early day of neutrophil engraftment [5]	1.4
Advanced disease status [26]	1.5-1.7		
Acute kidney injury [21]	NR		
Platelet refractoriness [21]	NR		
High INR [21]	NR		

Corbacioglu S et al. Biol Blood Marrow Transplant 25 (2019) 1271-1280

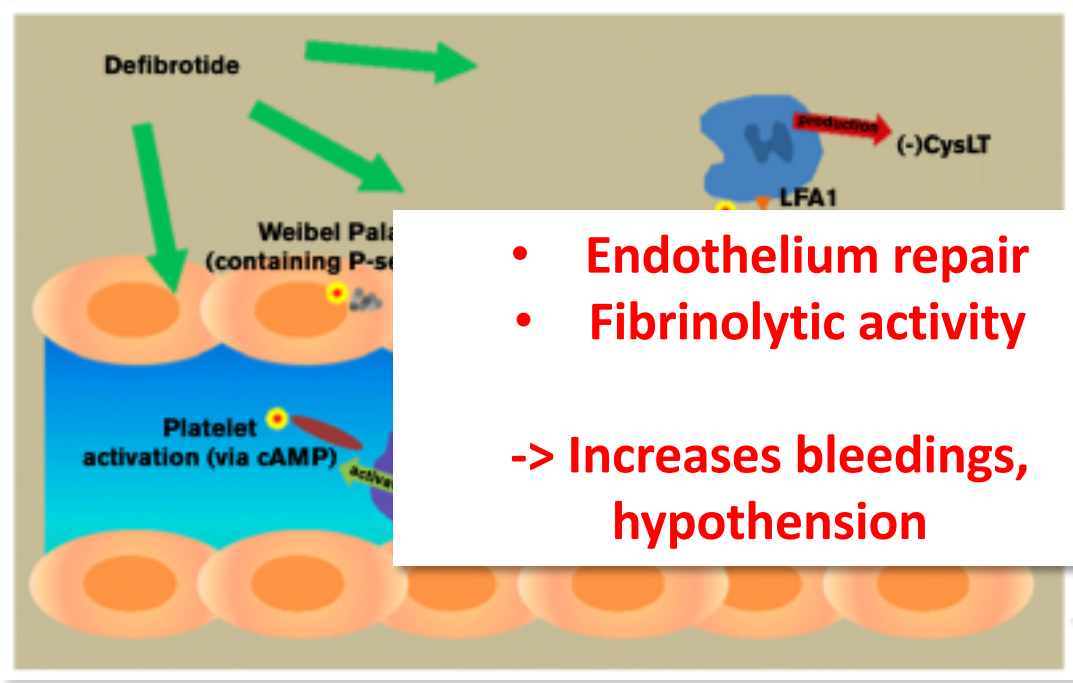
SOS/VOD biomarkers (proposed)

Hematological markers highly aspecific!

Biomarker
Broad-spectrum/multiple mechanism
Panel of changes in tumorogenicity-2, angiopoieten-2, L-ficolin, hyaluronic acid, and VCAM-1
↓ L-ficolin plasma level
Genetic polymorphisms
MTHFR C677T/A1298C
Heparanase single nucleotide polymorphisms
Hematologic and endothelial
↓ Protein C levels
↓ Antithrombin III levels
↓ Type III procollagen and tPA
↑ PAI-1 antigen levels
↑ Extra-cellular endothelial vesicles CD144*
↑ vWF, thrombomodulin, soluble IAM-1*
Hepatic/splenic
↑ Maximum total serum bilirubin/bilirubin increase at any point in time
↑ Total bilirubin, D-dimer
↑ Hepatocyte growth factors/with/without IL-6
↑ APRI
↑ Splenic volume
↑ Panel of liver fibrosis indices: APL APRI, PSR, FIB-4†
Inflammatory/immune response
↑ IL-6, IL-10, TNF-α plasma levels‡
↑ IL-6 plasma level at + day 7 post-HSCT
↓ IGF and IGFBP-3 plasma levels

Corbacioglu S et al. Biol Blood Marrow Transplant 25 (2019) 1271-1280

SOS/VOD treatment (Defibrotide)



- **Endothelium repair**
- **Fibrinolytic activity**

-> Increases bleedings, hypothension

Information and vascular permeability
- ↓CysLT release

…IFκB activation (bone …ow)

…latelet activation

…cyte adhesion molecules

…-selectin expression

…erferes with ICAM1/LFA1 …em

…bosis

…PA, TFPI, TM
- ↓PAI-1, PAF, thrombin

Cytokine production
- ↑PGE_2 and PGI_2
- ↓IL-6, VEGF, TXA_2, LTB4, TNF_α

HLA molecules
- ↓MHCI molecule expression
- ↓MHCII expression

Vascular tone
- Antagonizes endothelin 1
- ↑NO and NOS

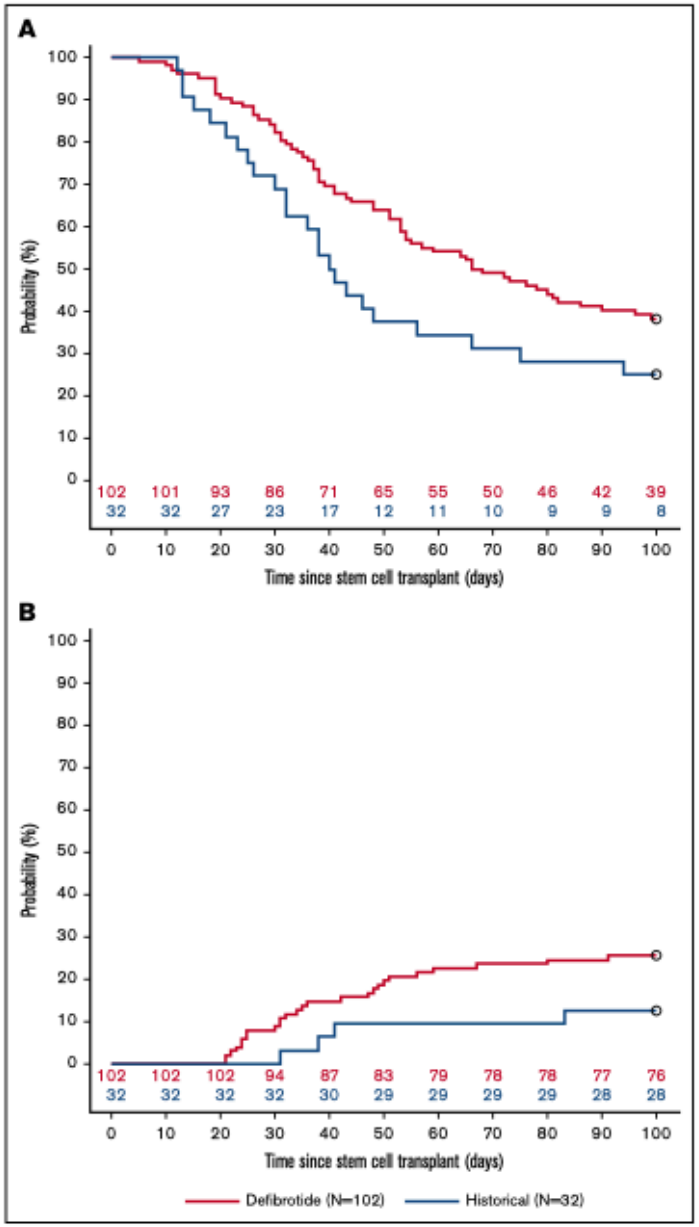
Richardson PG et al. Blood Adv 2018;2(12):1495-1509

Defibrotide phase 3 study

Primary end points of phase 3 study (not randomized) in defibrotide (6.25 mg/Kg every 6 hs, **25 mg/kg daily**) treated patients (n. 102) vs historical controls receiving supportive treatment.

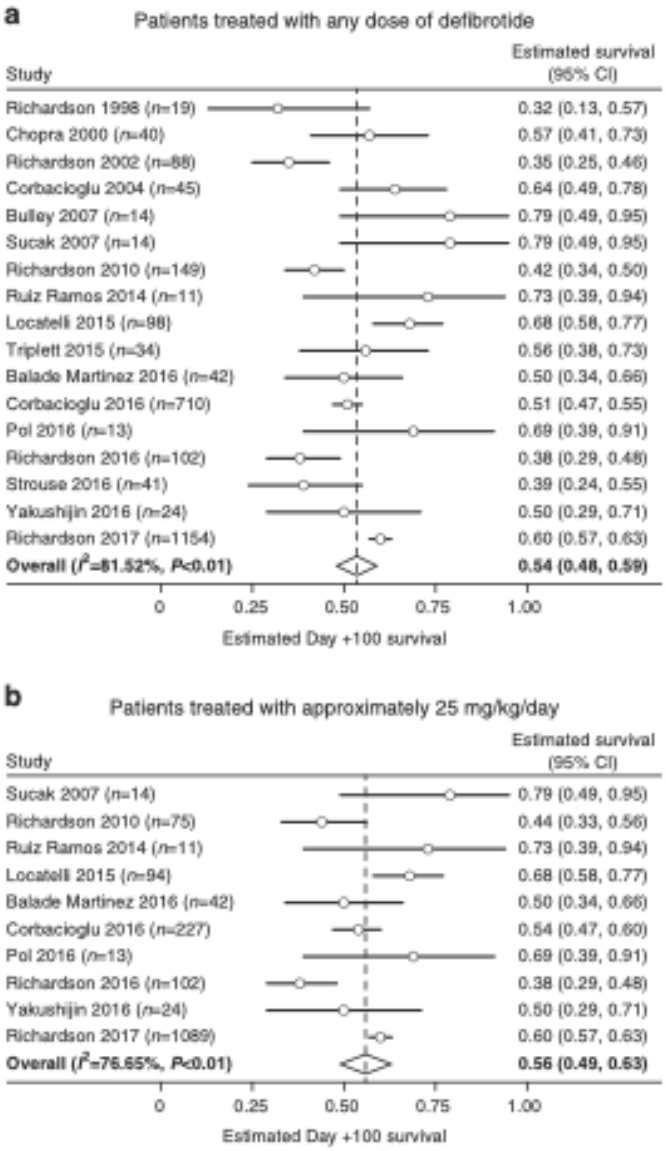
(A) Kaplan-Meier estimates of overall survival distribution

(B) Complete response (defined as total bilirubin < 2 mg/dL and resolution of MOD/MOF) <u>at day 100 following HSCT</u>



Richardson PG, et al . Blood. 2016;127(13):1656-1665.

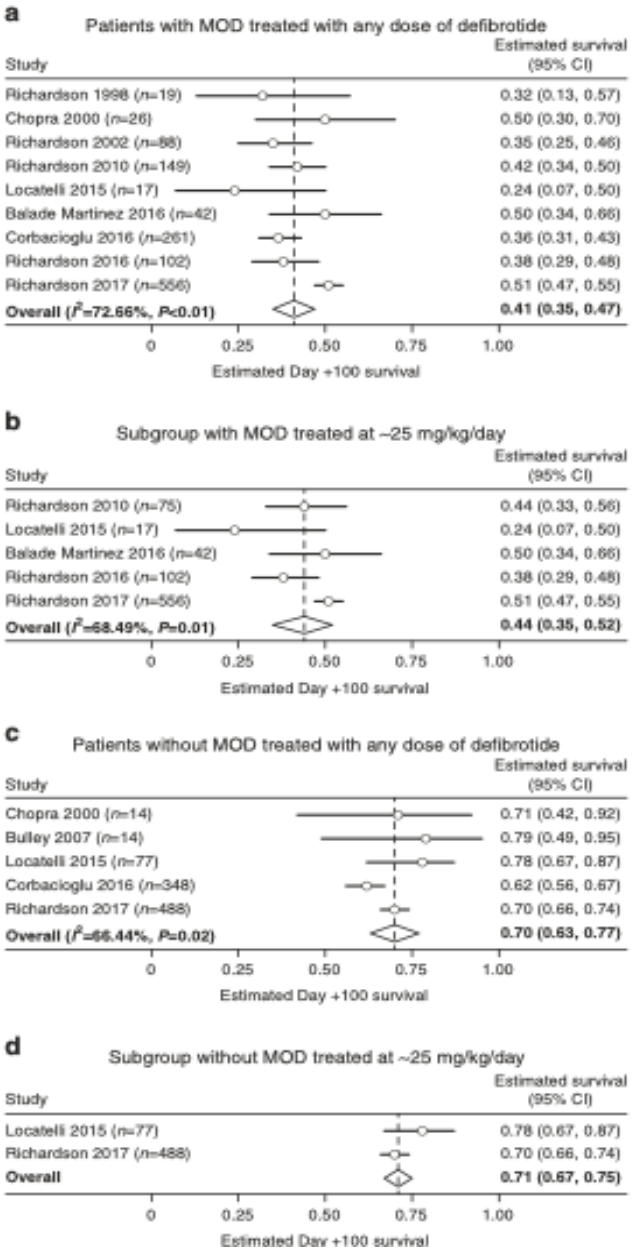
Defibrotide pooled analysis (I)



Pooled analysis of the estimated **Day + 100 survival rates** of the overall patient populations treated with any defibrotide dose or ~ 25 mg/kg/day

Richardson P et al. Bone Marrow Transplant. 2019 Feb 25. doi: 10.1038/s41409-019-0474-8. [Epub ahead of print]

Defibrotide pooled analysis (II)



Pooled analysis of the estimated **Day + 100 survival** for patients **with MOD and without MOD**

Richardson P et al. Bone Marrow Transplant. 2019 Feb 25. doi: 10.1038/s41409-019-0474-8. [Epub ahead of print]

Can we prevent SOS/VOD?

The HARMONY Trial

Clinicaltrials.gov. NCT02851407: Study comparing efficacy and safety of **defibrotide vs best supportive care** in the prevention of hepatic veno-occlusive disease in adult and pediatric patients.

Available from:
https://clinicaltrials.gov/ct2/show/NCT02851407.

Early/Late allo-HSCT life-threatening complications

Group of complications without well-established origins, clically characterized by thrombosis and/or bleeding and MOF

- **Sinusoidal Obstruction Syndrome/VOD**
- Capillary Leak Syndrome
- Engraftment Syndrome
- **Transplant-Associated Microangiopathy (TAM)**
- Diffuse Alveolar Haemorrhage (DAH)
- Idiopathic Pneumonia Syndrome

Early onset after HSCT, overlapping clinical manifestations, the absence of well-defined clinical criteria for diagnosis (and consequently an unknown true incidence), the absence of well-established treatments, and the tendency to evolve to an irreversible multiorgan dysfunction syndrome

TMA: Clinical/Lab presentation

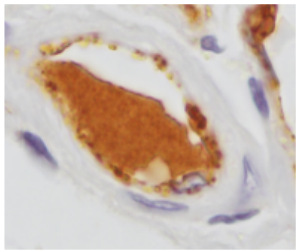
Q. Thrombotic occlusion of the microvasculature (often asy-oligosymptomatic), from different causes, leading to:

- **Hemolytic anemia with elevation of LDH and negative direct Coomb's test**
- **Thrombocytopenia**
- **Fragmentation of red blood cells -> Schistocytes**
- Normal baseline coagulation (lab)

Thrombotic MicroAngiopathies (TMAs)

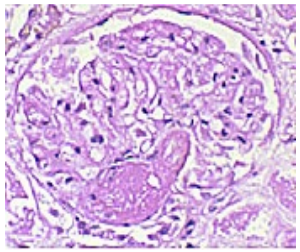
TMAs – Costellation of diseases for unique symptoms

ADAMTS13 Deficiency



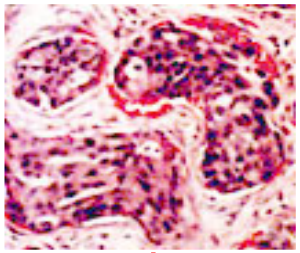
VWF-platelet Aggregate

DIC



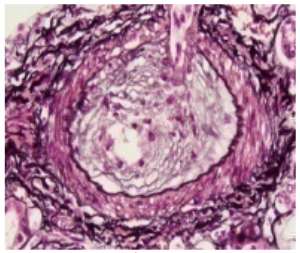
Fibrin Clot

Metastasizing Cancer



Tumor Cells

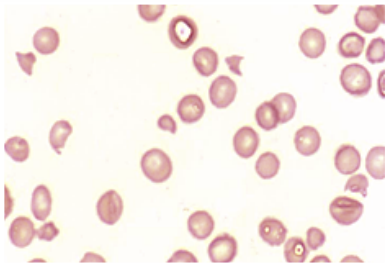
Shiga toxins, T-Ag Activation
Uncontrolled Complement Activation
Lupus, Scleroderma



Microangiopathy

1. Microvascular Thrombosis or Stenosis

2. Thrombocytopenia



High Shear Stress

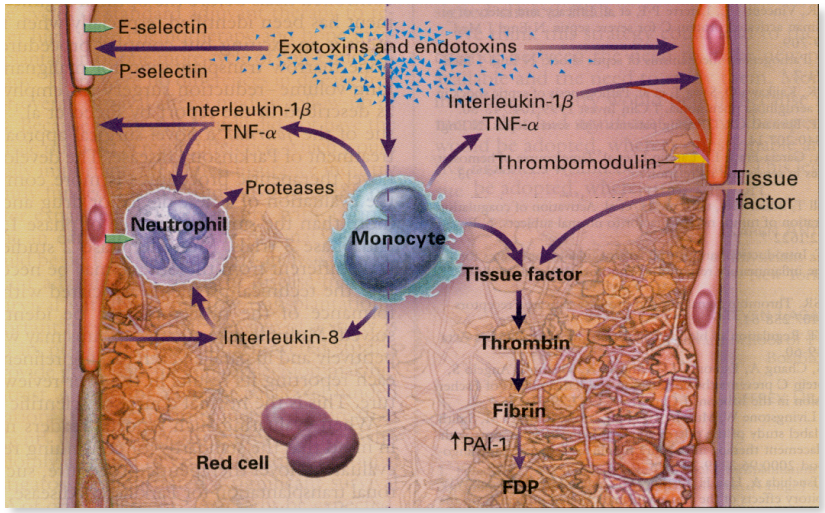
Erythrocyte Fragmentation

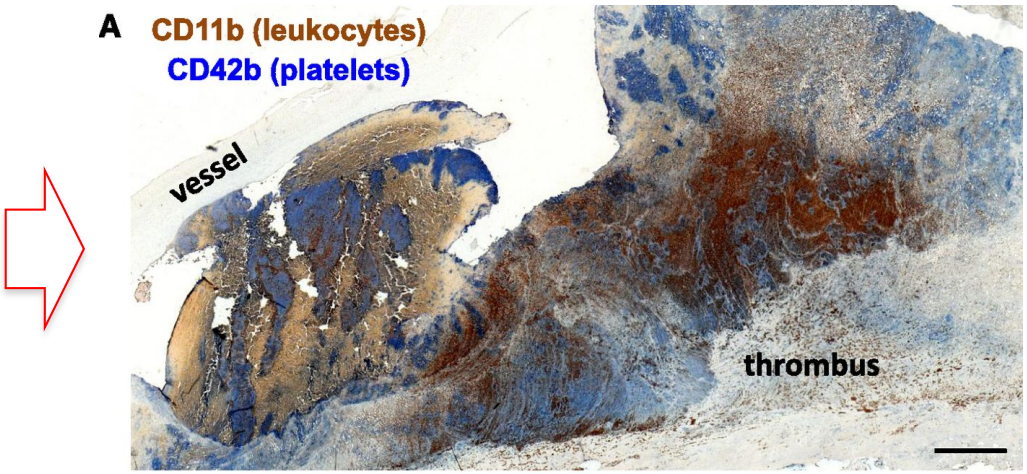
3. Organ injury

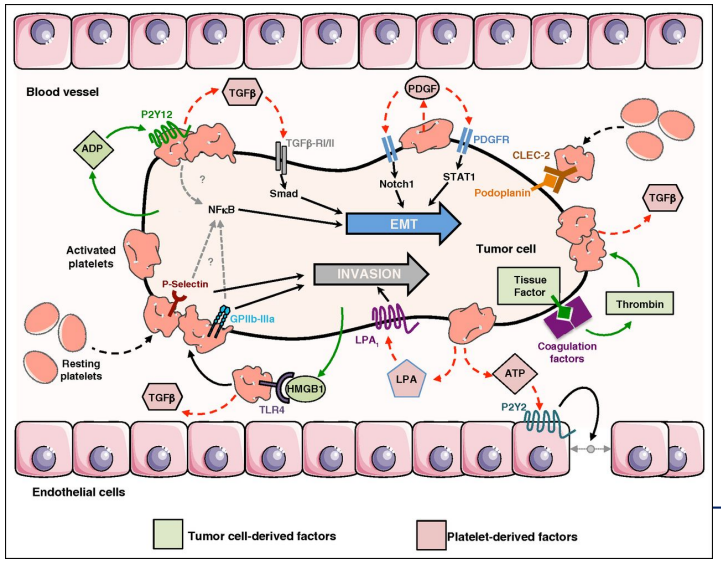
- Neurologic deficits, DMS
- Hematuria. renal failure
- Heart failure
- Pancreatitis
- Abd pain, N/V, diarrhea

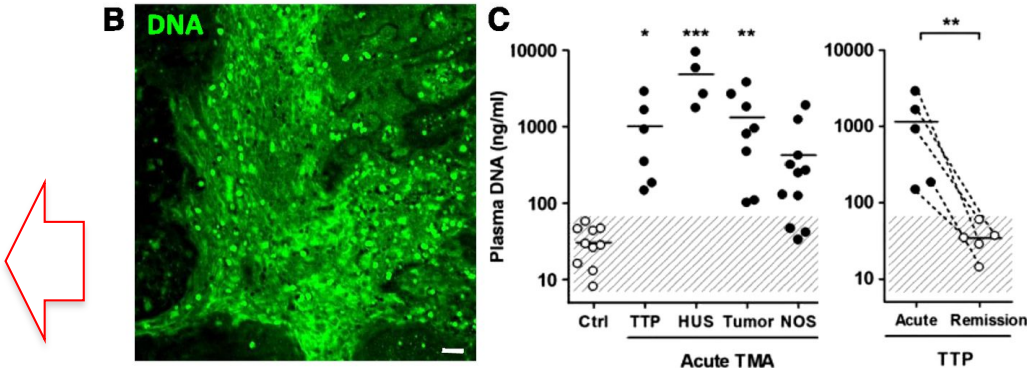
Tsai HM, Sem Thromb Hemost 2012

Interaction between coagulation factors, leukocytes & platelet in cancer/inflammation



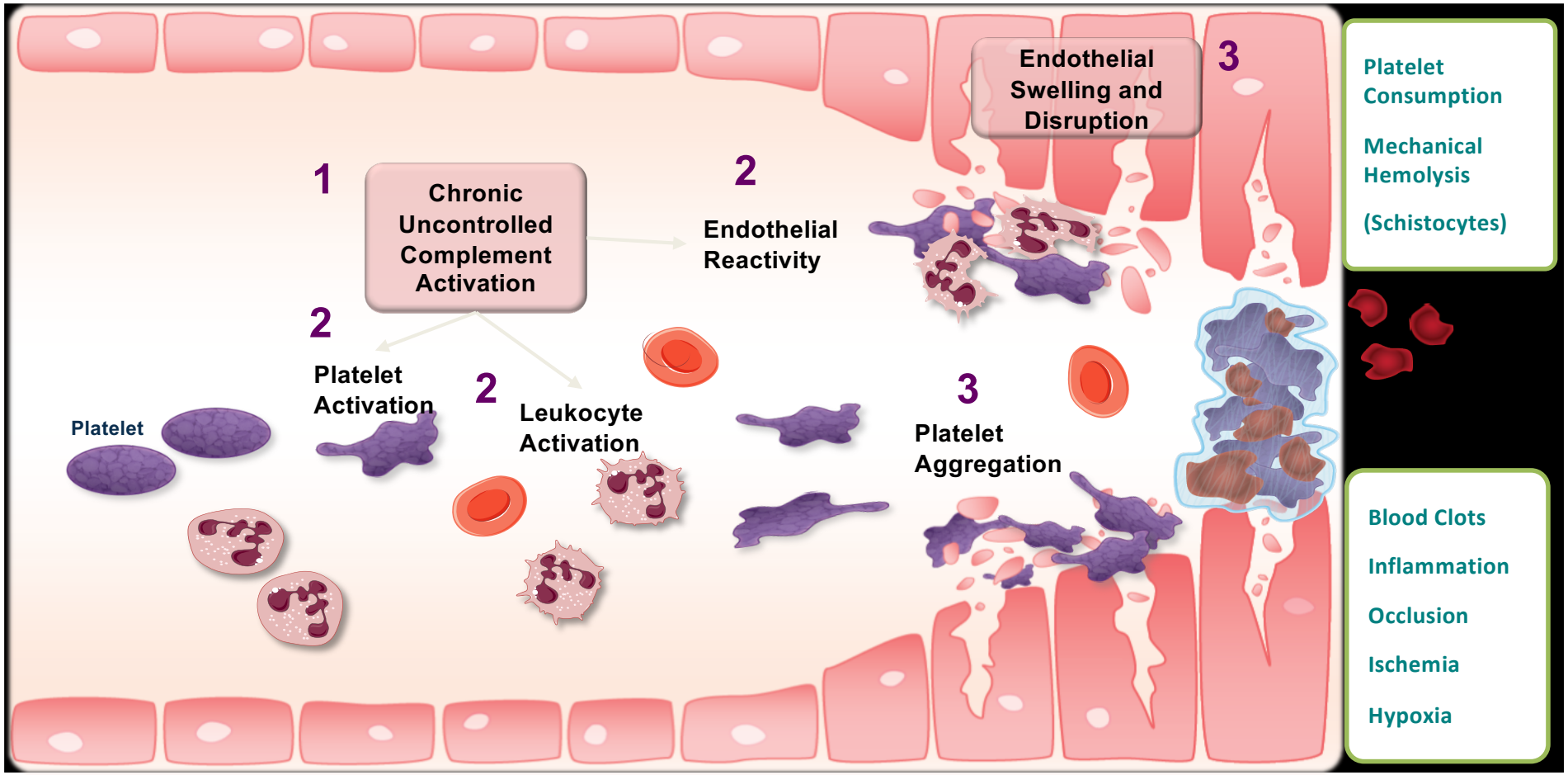






Byrnes JR et al. Blood 2017;130:1795-1799

Link beteween Uncontrolled Complement, Platelet, Endothelial, and Leukocyte Activation Leading to TMA



Modified from Desch K et al. *JASN*. 2007;18:2457-2460. Modified from Licht C et al. *Blood*. 2009;114:4538-4545. Modified from Noris M et al. *NEJM*. 2009; 361:1676-1687. Modified from Stahl A et al. *Blood* 2008;111:5307-5315. Modified from Camous L et al. *Blood*. 2011;117:1340-1349.

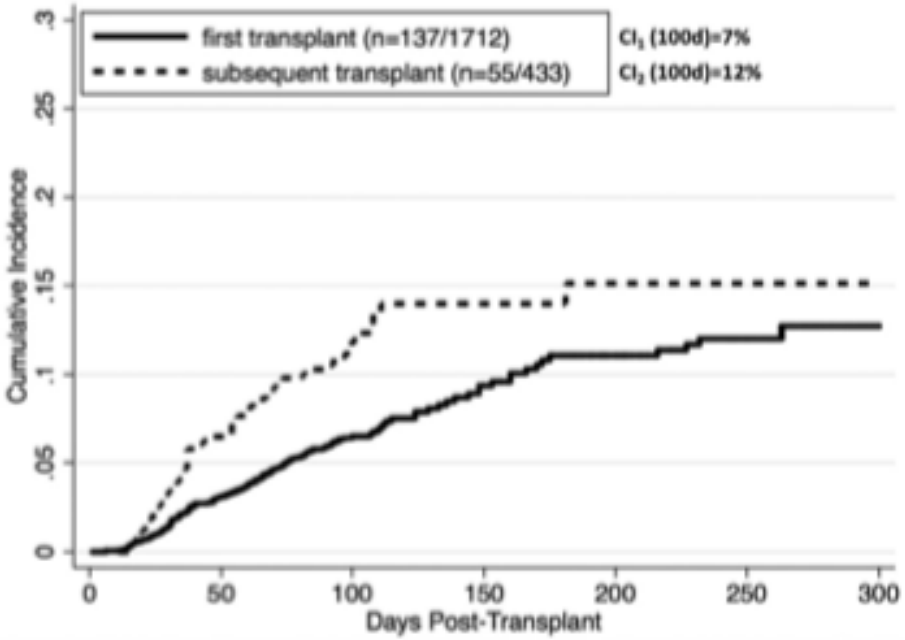
TMAs other than TTP

Disorder	Pathophysiology
TMA–Shiga toxin mediated	Direct endothelial damage with apoptosis due to effects of Shiga toxin
TMA–complement mediated	Endothelial damage from unregulated complement activation resulting from the development of anti–factor H autoantibodies or mutations leading to abnormal complement regulatory proteins or abnormal complement factors
TMA–hematopoietic stem cell transplantation associated	Endothelial damage due to infection, chemotherapy, radiation therapy, or graft-versus-host disease due to transplant. Of note, a significant percentage of affected pathway
TMA–drug associated	Mechanism varies depending on drug and includes direct endothelial damage as well as the development of ADAMTS13 autoantibodies
TMA–malignancy associated	Activation of coagulation by tumor tissue factor expression. Possible complement regulatory pathway mutations
TMA–*Streptococcus pneumonia* associated	Exposure of normally hidden endothelial antigens by bacterial neuramidase resulting in complement mediated endothelial damage
TMA–coagulation mediated	Mutations in DGKE, plasminogen, and thrombomodulin resulting in thrombosis and complement activation
HELLP syndrome	Mutations in alternate complement pathway regulatory elements

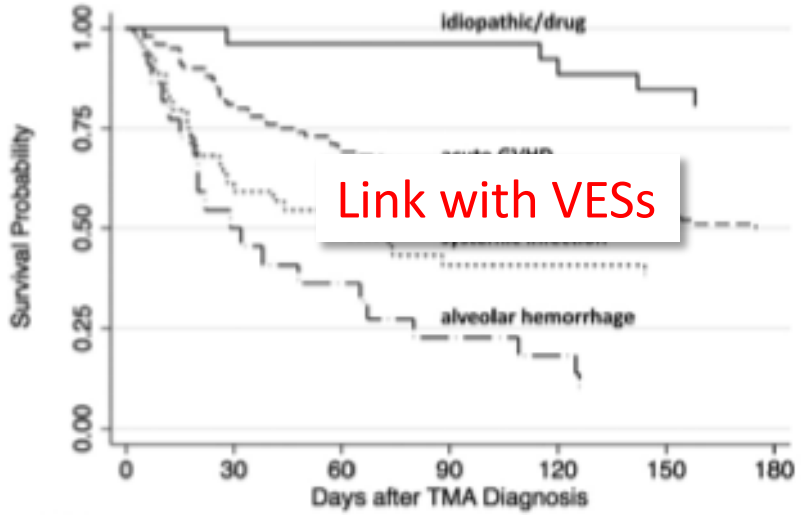
All these 3 conditions are present in allo-HSCT

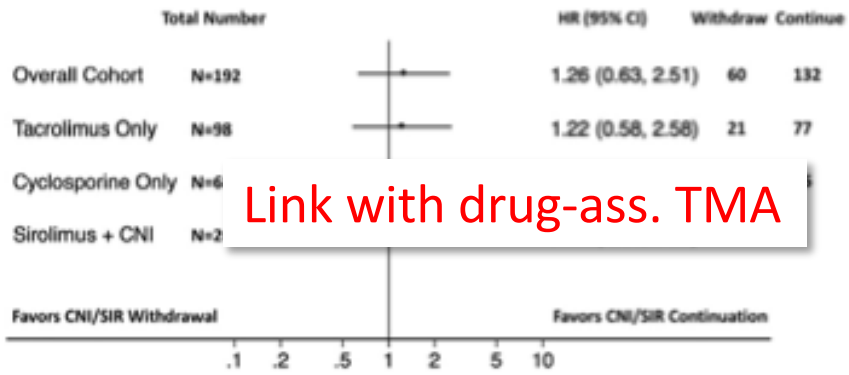
Winters JL. Hematology 2017;632-8

HSCT-related TMA



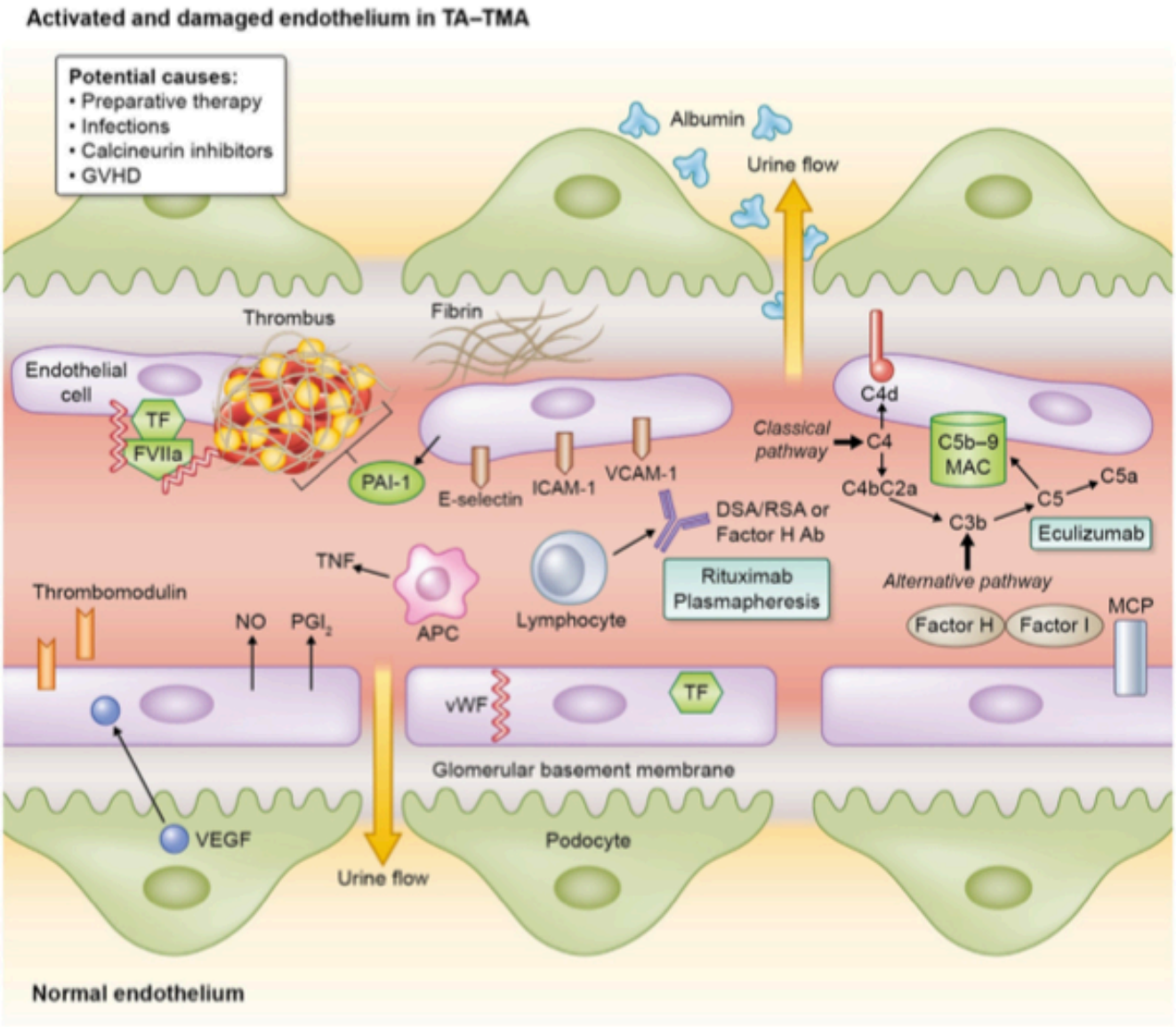
Overall incidence **7.6%** (2.564 pts)





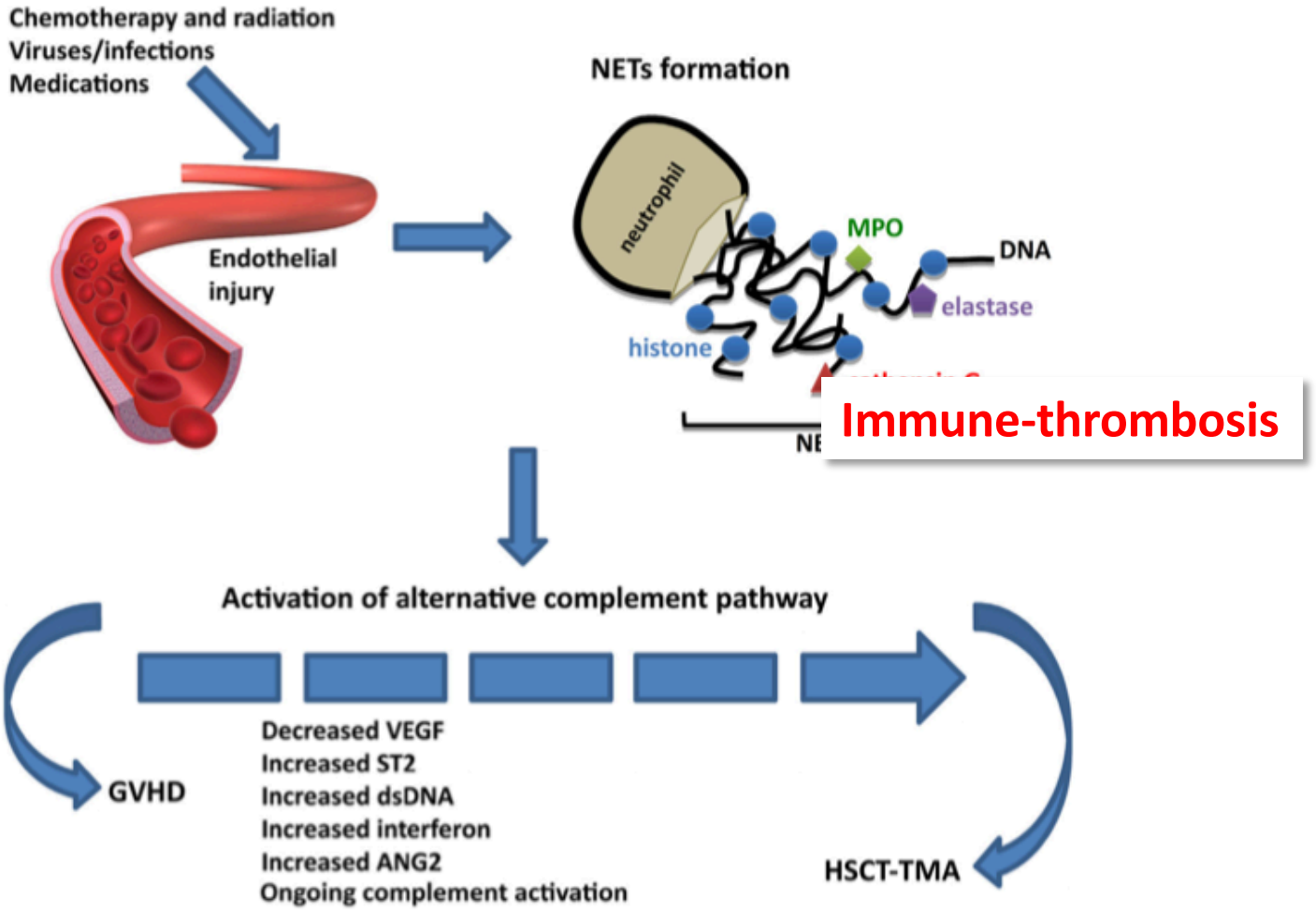
Ang L et al. Biol Blood Marrow Transplant 2019;25:570-576

HSCT-mediated TMAs (glomerular endothelium)



Wanchoo R et al. Am J Kidney Dis. 2018;72(6):857-865

Proposed mechanism of how GVHD could be linked with HSCT-TMA



Wanchoo R et al. *Am J Kidney Dis.* 2018;72(6):857-865

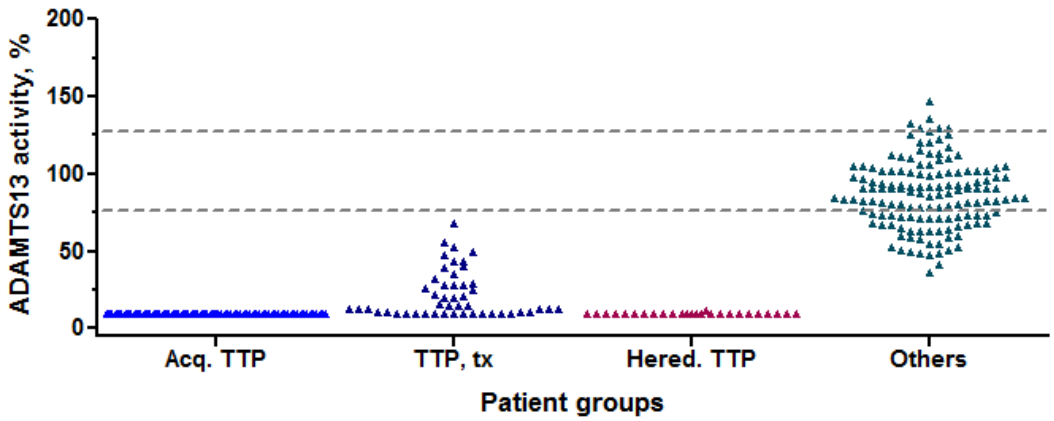
How to distinguish (lab/clinical) TMAs?

Lab (no too much):

- **> ADAMTS13** for ruling out TTP
- Coag. test for ruling out DIC in some cases (complement testing unusefull)

Clinic (even less):

- > some differences among cancer-related TMAs (but not others)



	Cancer-associated thrombotic microangiopathy	Chemotherapy-associated thrombotic microangiopathy
Disseminated cancer	Yes	No
Renal involvement	Mild/absent	Mild/severe
Disseminated intravascular coagulopathy	Present	Absent
Circulating erythroblasts	Present	Absent
Clinical presentation	Thrombotic thrombocytopenic purpura-like disease	Hemolytic-uremic syndrome-like disease
Treatment	Chemotherapy	Stop chemotherapy Supportive care Specific treatments

Grange S et al. Nephrologie & Therapeutique 13S (2017) S109–S113

Can we prevent allo-HSCT-related TMA?

Table 1. Patients' characteristics

	Danaparoid (n = *164*)	*Dalteparin* (n = *59*)	P-*value*[a]
Age, years, median (range)	48 (16–70)	36 (17–61)	< 0.001
Gender: male/female, *n*	107/57	36/23	0.64
Year of stem cell transplantation			< 0.0001
January 2004–March 2008	0	59	
April 2008–January 2013	164	0	
Diagnosis, n *(%)*			
AML	76 (46.3)	22 (37.3)	0.28
ALL	27 (16.5)	19 (32.2)	0.01
CML	3 (1.8)	3 (5.1)	0.19
MDS	22 (13.4)	5 (8.5)	0.36
ML	20 (12.2)	5 (8.5)	0.63
ATLL	8 (4.9)	2 (3.4)	1
MM	1 (0.6)	0 (0)	1
SAA	7 (4.3)	3 (5.1)	0.73
Disease risk status at transplantation, n *(%)*[b]			
Standard risk	109 (66.5)	35 (59.3)	0.34
High risk	55 (33.5)	24 (40.7)	
Conditioning regimen, n *(%)*			
MAC	77 (47.0)	51 (86.4)	< 0.001
TBI-based	66 (40.3)	44 (74.6)	< 0.001
BU-based	11 (6.7)	7 (11.8)	0.26
RIC	87 (53.0)	8 (13.6)	< 0.001
FLU+LPAM-based	84 (51.2)	6 (10.2)	< 0.001
FLU+Cy-based	3 (1.8)	2 (3.4)	0.61
Donor type, n *(%)*			
Matched related	37 (22.6)	19 (32.2)	0.16
Matched unrelated	30 (18.3)	15 (25.4)	0.26
Mismatched related	7 (4.3)	5 (8.5)	0.31
Mismatched unrelated	90 (54.9)	20 (33.9)	0.006
ABO mismatched donor, *n* (%)	97(59.1)	33(55.9)	0.76
Cell sourse, n *(%)*			
Bone marrow	64 (39.0)	40 (67.8)	0.002
Peripheral blood	36 (22.0)	13 (22.0)	1
Cord blood	64 (39.0)	6 (10.2)	< 0.001
Before allogeneic HCT, *n* (%)	20 (12.2)	4 (6.8)	0.33
GvHD prophylaxis, *n* (%)			< 0.001
CSA+MTX	37 (22.6)	31 (52.5)	
Tacrolimus+MTX	127 (77.4)	28 (47.5)	
Acute GvHD, *n* (%)			0.2
Grade 0–I	113 (68.9)	35 (59.3)	
Grade II–IV	51 (31.1)	24 (40.7)	
Cytomegalovirus viremia, *n* (%)	96 (58.5)	28 (47.5)	0.17

Table 2. Clinical factors predicting for TMA from univariate and multivariate analyses by using fine-gray proportional hazards model

Variables	*Univariate*		*Multivariate*[a]	
	HR (95% CI)	P-*value*	*HR (95% CI)*	P-*value*
Danapaloid	0.46 (0.23–0.94)	0.03	0.34 (0.16–0.75)	0.007
Age >50 years	0.68 (0.31–1.47)	0.33		
Female	1.18 (0.57–2.44)	0.65		
Lymphoid malignancy	2.42 (1.18–4.96)	0.02	2.42 (1.14–4.78)	0.02
High-risk disease status	3.49 (1.67–7.28)	0.0009	2.52 (1.21–5.23)	0.01
Reduced intensity conditioning	0.77 (0.37–1.61)	0.48		
TBI-based	1.39 (0.67–2.88)	0.37		
BU-based	1.95 (0.65–5.81)	0.23		
Unrelated donor	2.34 (0.91–6.05)	0.08	2.46 (0.94–6.46)	0.07
HLA mismatched donor	1.54 (0.75–3.18)	0.24		
ABO mismatched donor	1.24 (0.59–2.60)	0.57		
Cord blood	1.53 (0.74–3.17)	0.25		
Before allogeneic HCT	4.40 (1.99–9.71)	0.0003	3.60 (1.51–8.60)	0.004
Tacrolimus	0.75(0.36–1.57)	0.44		
Cytomegalovirus viremia	0.58(0.28–1.19)	0.14		
aGvHD: Grade II–IV	0.97 (0.46–2.07)	0.94		

Danaparoid 1.250 U b.i.d. vs LMWH 3.000 U/die
1 -> 28 days from allo-HSCT

Machida S et al. Bone Marrow Transplantation (2017) 307 – 309

HSCT-related TMA: Can we satisfactory treat?

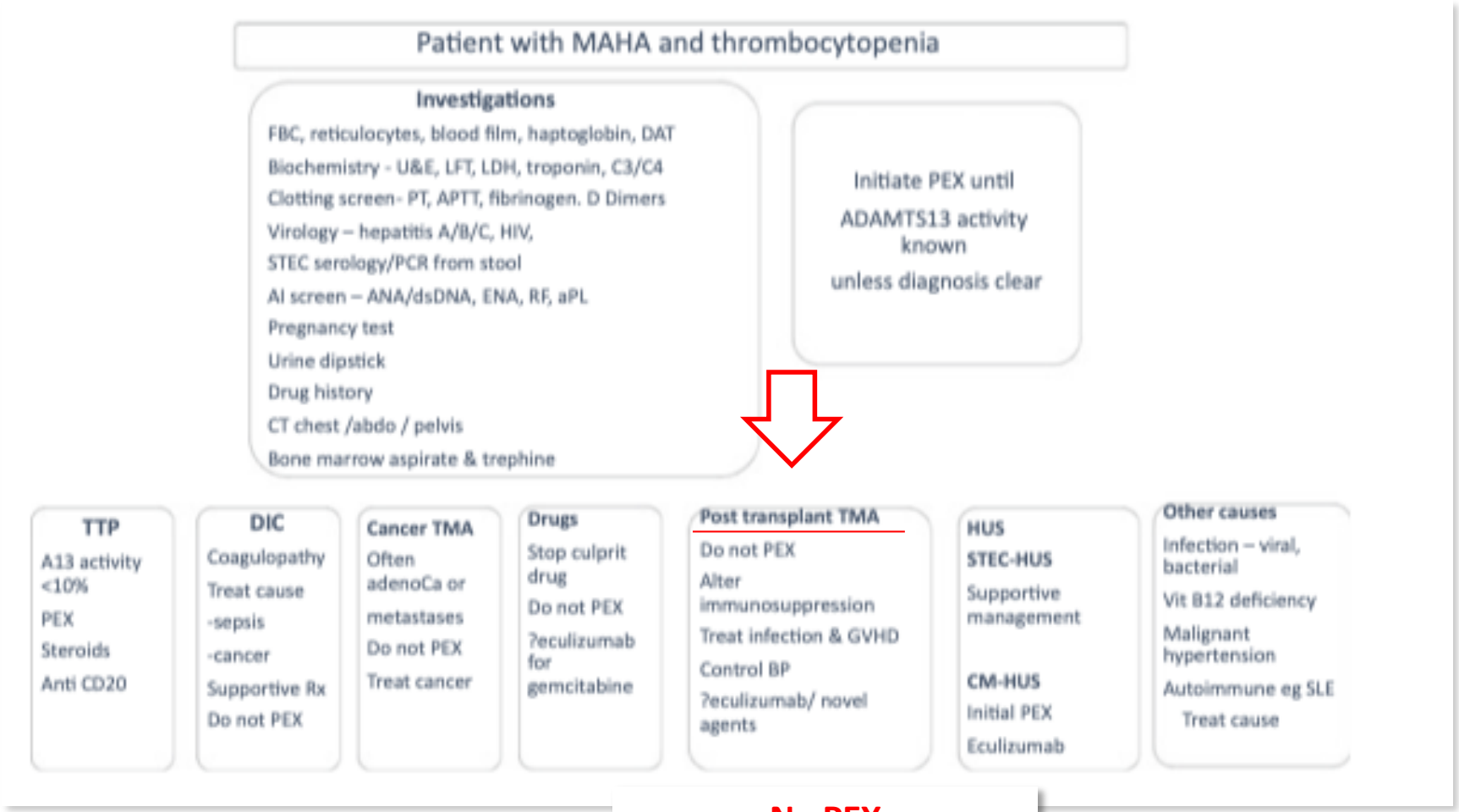
(as well as novel therapies)

Table 1. Summary of Treatment Strategies Used and Being Studied for HSCT-TMA

Treatment Modality	No. of Patients in Published Reports	Mechanism	Response Rate
Plasmapheresis	162 (adults)	Removal of potential inhibitor/antibody	59%-65%
Daclizumab	13 (adults)	Anti–IL-2	69%
Rituximab	15 (8 adult, 7 pediatric)	Anti-CD20	80%
Defibrotide[c]	16 (11 adult, 5 pediatric)	Antifibrinolytic and thrombotic	67%
Vincristine	16 (13 adult, 3 pediatric)	Antimicrotubular agent, immumomodulator	69%
Eculizumab	34 (24 pediatric, 1 adult, & 1 study w/ 9 cases w/ age range of 2-61 y)	C5 inhibitor	67%

Wanchoo R et al. Am J Kidney Dis. 2018;72(6):857-865

Proposed approach in HSCT-related TMAs



M Scully. 2019. Thrombosis and Hemostasis in Cancer, Cancer Treatment and Research 179, https://doi.org/10.1007/978-3-030-20315-3_10

Lessons from VESs/TMAs

VESs/TMAs are variable entities in presentation and course:

- Distinction among TMAs is not clinically feasible
- Distinction among VESs is not clinically feasible
- Thrombocytopenia may not be profound in severe cases
- **Organ dysfunction may result directly** from vascular injury and increased permeability without thrombosis or vascular stenosis
- Absence of reliable biomarkers (except TTP)
- Treatment of TMAs other than TTP is still unsatisfactory
- Treatment of severe SOS/VOD (**Defibrotide**) should start asap (Baltimore criteria)