Microangiopatie Trombotiche nel Trapianto di Cellule Staminali Emopoietiche

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A.O.U. di Perugia

Perugia, 29 Settembre 2016

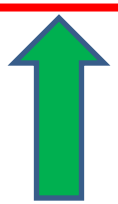
SYNDROMES of THROMBOTIC MICROANGIOPATHY

CLINICAL FEATURES

- Microangiopathic hemolytic anemia;
- Thrombocytopenia;
- Organ injury.

PATHOLOGIC FEATURES

- Vascular and endotelium damage;
- Arteriolar and capillary thrombosis.



HEMOPOIETIC STEM CELL TRANSPLANTATION

Blood and Marrow Transplant Clinical Trials Network Toxicity Committee Consensus Summary: Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplantation

Vincent T. Ho, Biology of Blood and Marrow Transplantation 11:571-575 (2005)

REVIEW

Diagnosis and treatment of transplantation-associated thrombotic microangiopathy: real progress or are we still waiting?

ED Batts[1,2,3] and HM Lazarus[1] Bone Marrow Transplantation (2007) 40, 709–719

EDITORIAL

Hematopoietic stem cell transplantation-associated thrombotic microangiopathy: defining a disorder

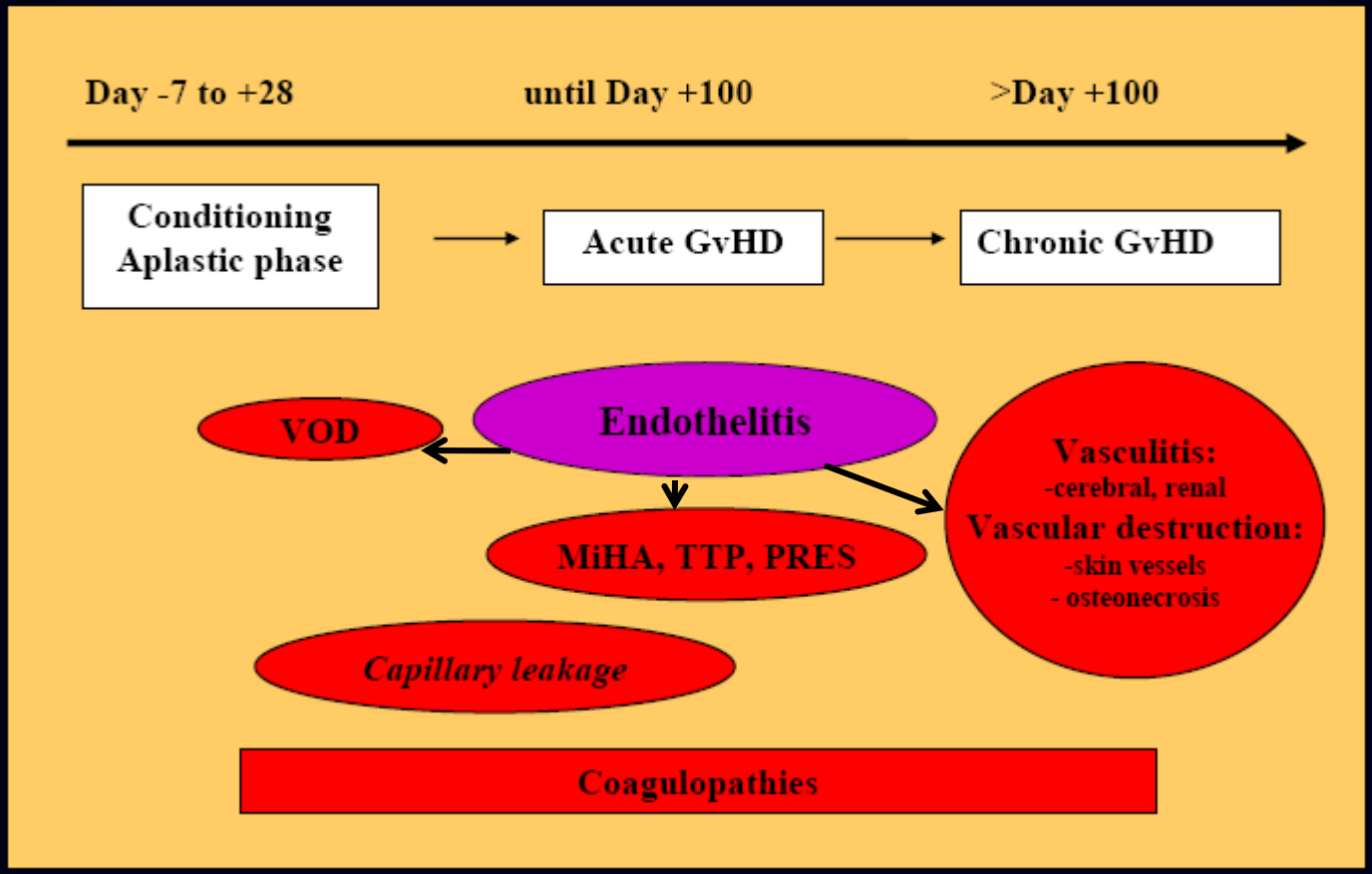
JN George Bone Marrow Transplantation (2008) 41, 917–918

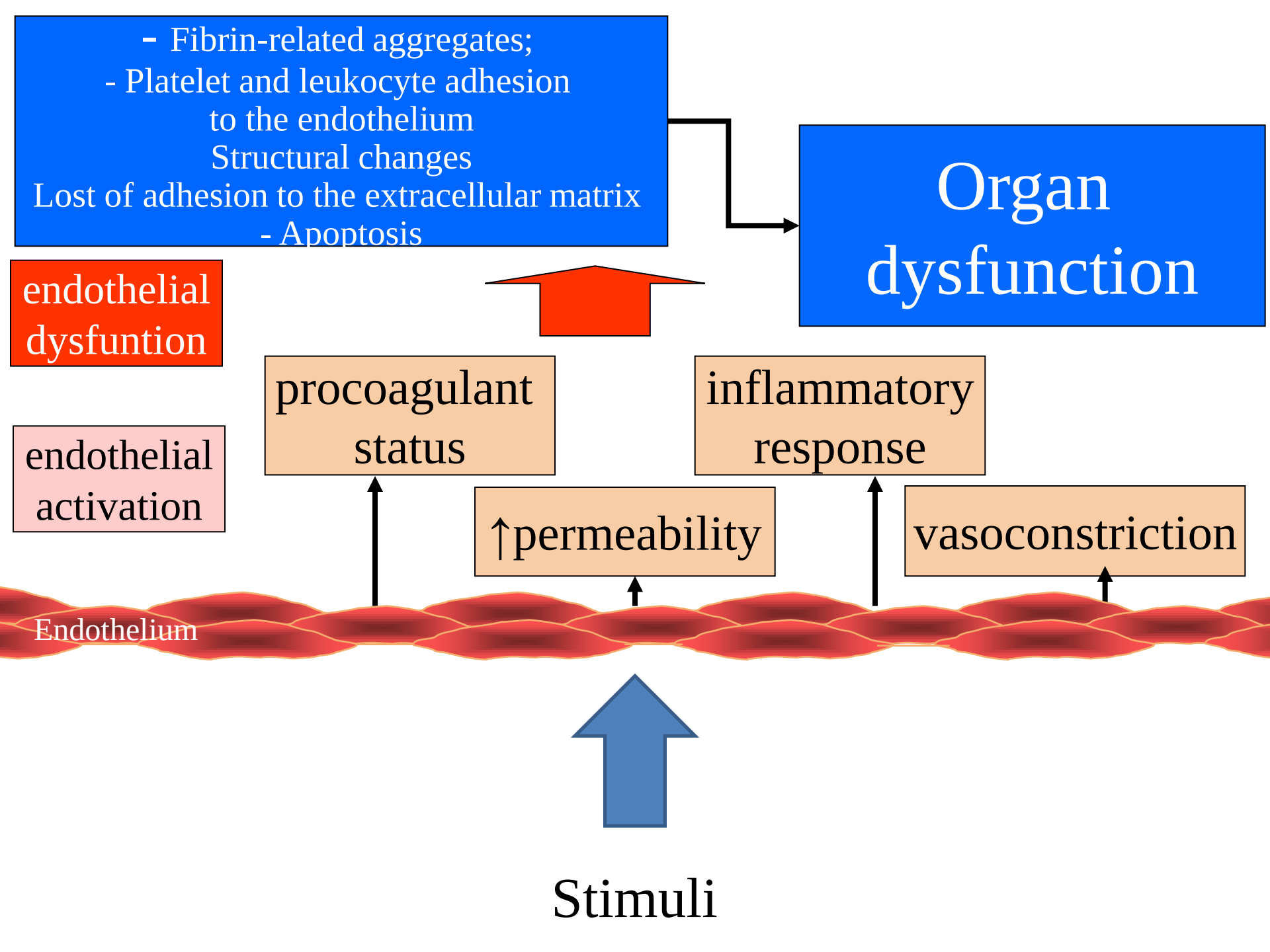
Hemopoietic stem cell trasplantation Thrombotic Microangiopathy (TA-TMA)

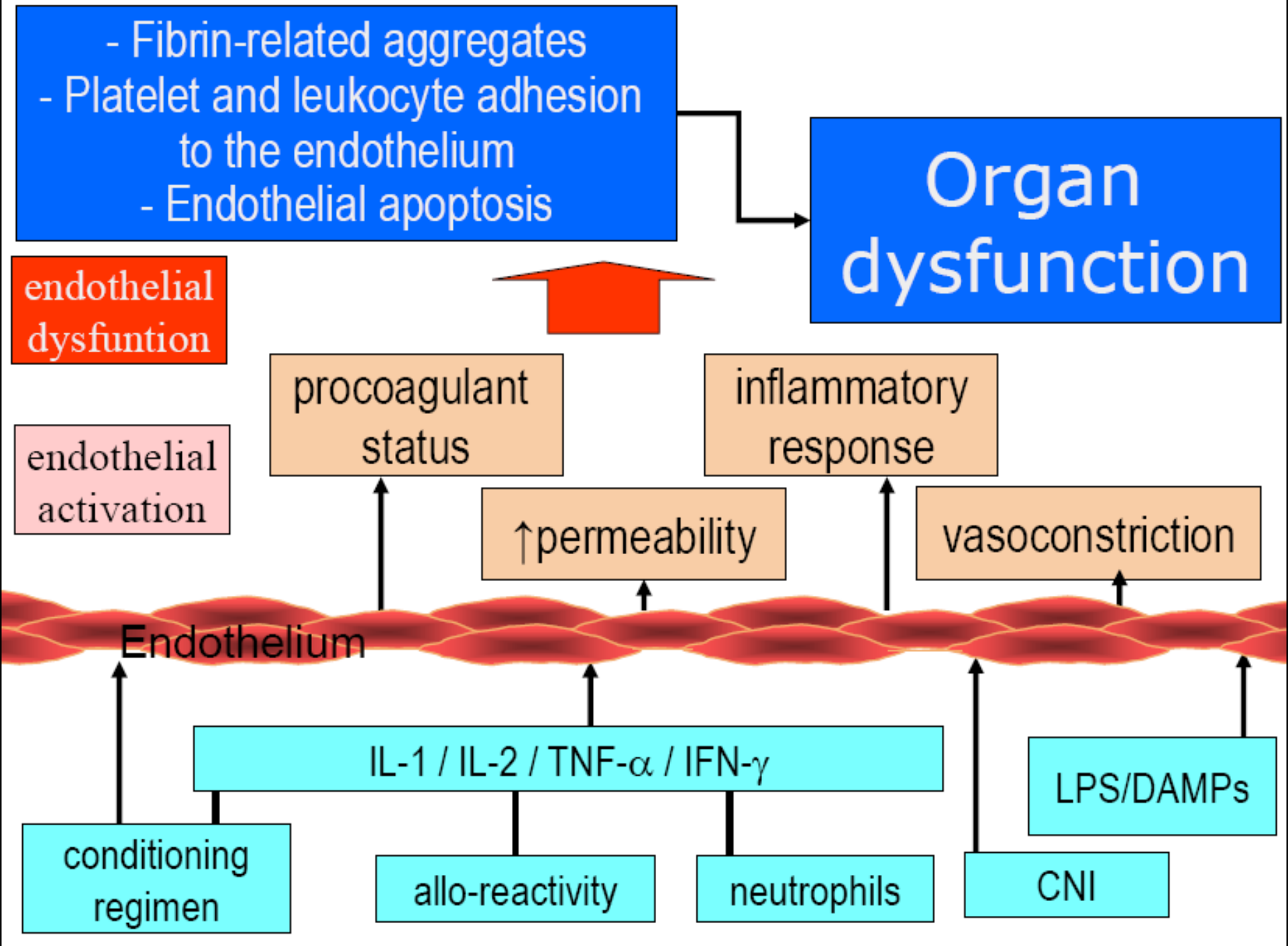
- Severe complication of HSCT (auto and allo);
- Incidence, aetiology, diagnostic criteria, classification and treatment: lack of true consensus;
- Reported incidence varied enormously from 0,5 to 76%, due to use of different diagnostic criteria;
- Median time to onset after transplant 30-45 D;
- TA-TMA can range from a mild, self-limited form to uncontrollated fulminat disease leading to death (mortality rates 60-90%);
- TA-TMA is a multifactorial disease where generalised endothelial disfunction leads to microangiophatic hemolitic anemia, intravascular platelet activation, and formation of platelet-rich thrombi within the circulation.

Endothelial complications after HSCT

Time course within different HSCT phases




- Fibrin-related aggregates;
- Platelet and leukocyte adhesion to the endothelium
Structural changes
Lost of adhesion to the extracellular matrix
- Apoptosis
Organ dysfunction
endothelial dysfuntion
procoagulant status
inflammatory response
endothelial activation
↑permeability
vasoconstriction
Endothelium
Stimuli


- Fibrin-related aggregates
- Platelet and leukocyte adhesion to the endothelium
- Endothelial apoptosis
Organ dysfunction
endothelial dysfuntion
procoagulant status
inflammatory response
endothelial activation
↑permeability
vasoconstriction
Endothelium
IL-1 / IL-2 / TNF-α / IFN-γ
LPS/DAMPs
conditioning regimen
allo-reactivity
neutrophils
CNI

Hemopoietic stem cell trasplantation TA-TMA

Mechanisms of ENDOTHELIAL DAMAGE

Conditioning regimens

Allogeneic >> Autologous

Myeloablative conditioning regimens = Reduced intensity regimens

Busulfan, fludarabine, platinum-based chemotherapies

TBI-based regimens

Endothelium damage during conditioning regimen

Murine model:

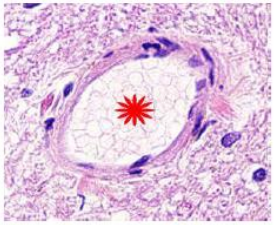
- Radiation with 7,5 GY causes intracellular edema and occlusion of microvascular lumens by edematous Ecs.

Samlowski WE et al, Lab Invesr 1987

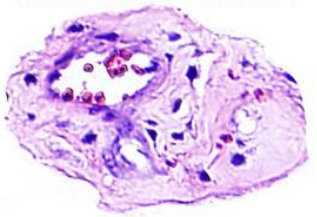
- CTX or MTX cause apomorphosis hydropsia and cytomembrane damage in ECs and increase the number of circulating ECs.

Zeng L et al. Transplant Proc 2008

Normal capillary[3]



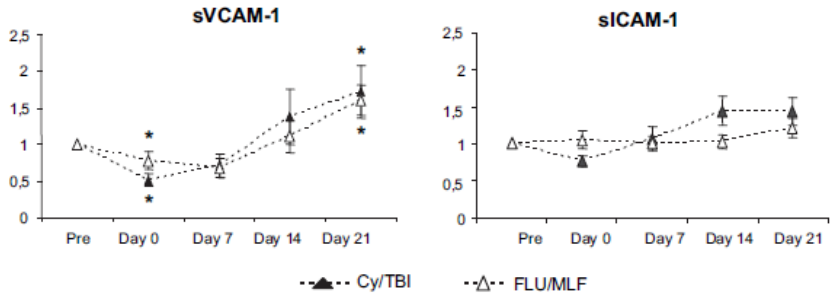
Radiation damage[3]



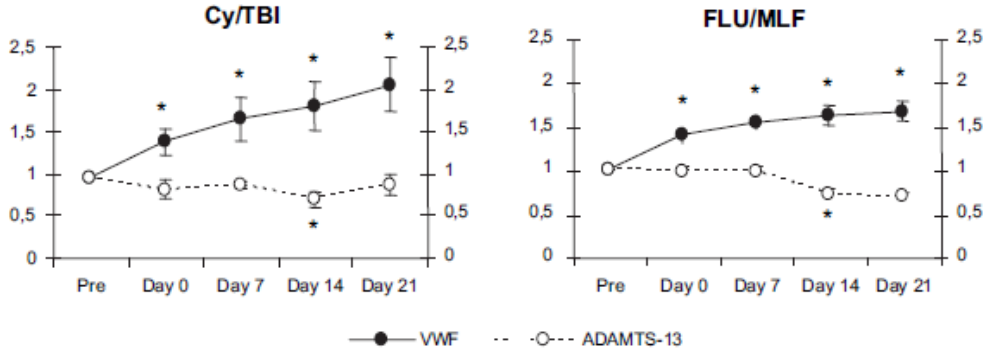
* = p< 0.05

Human studies:

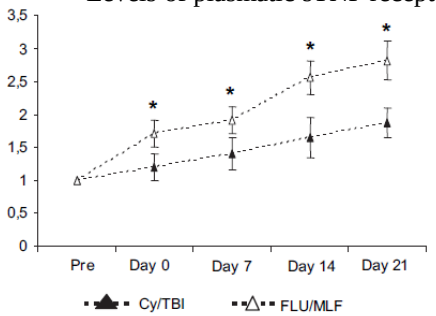
- Intensity of conditioning regimen correlates with endothelial damage by plasma level of: VWF, thrombomodulin, soluble forms of adhesion molecules (sVCAM-1, sICAM-1) , s TNF receptor I, ADAMTs 13,cyclic GMP



Palomo M, BBMT 2010
46 pts



Levels of plasmatic sTNF receptor 1



Comparison of thrombotic microangiopathy after allogeneic hematopoietic cell transplantation with high-dose or nonmyeloablative conditioning

E Willems Bone Marrow Transplantation (2010) 45, 689–693

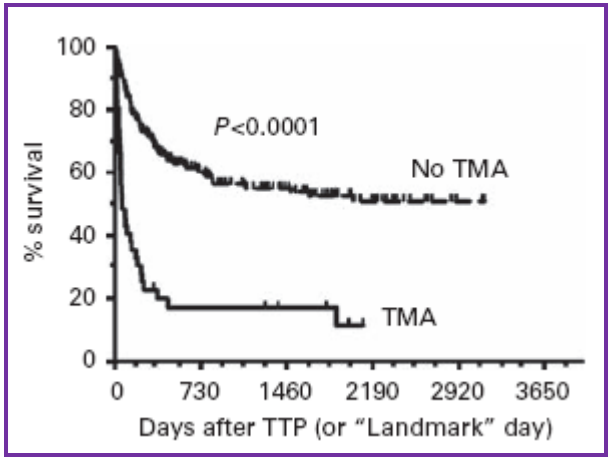
Table 3 Clinical factors predicting for TMA in a multivariate Cox model

	Hazard ratio (95% CI)	P-*value*
Grade 3–4 acute graft-versus-host disease	2.3 (1.5–3.5)	<0.0001
Nonmyeloablative versus high-dose conditioning	0.56 (0.36–0.88)	0.0121
Major ABO mismatch	0.76 (0.52–1.11)	0.15
Minor ABO mismatch	1.2 (0.9–1.8)	0.25
Unrelated donor	1.6 (1.1–2.2)	0.014
1/6 HLA-antigen mismatch	1.1 (0.6–2.0)	0.78
Patient age[a]	1.01 (1.00–1.03)	0.045
Prior HCT	0.82 (0.56–1.2)	0.33
Tacrolimus or cyclosporine as GVHD prophylaxis	0.73 (0.47–1.1)	0.16
Sirolimus administration	0.8 (0.36–1.8)	0.59

Table 1 Continued

	Myeloablative conditioning (n = 111)	*Nonmyeloablative conditioning (n = 176)*
TMA as primary cause of death; no. of patients (%)	1 (0.9)	2 (1.1)
TMA as secondary cause of death; no. of patients (%)	4 (3.6)	6 (3.4)

Abbreviations: ATG = anti-thymocyte globulin; CSP = cyclosporine; MDS = myelodysplastic syndrome; MMF = mycophenolate mofetil; MM = multiple myeloma; MPD = myeloproliferative disorder; RCC = renal cell carcinoma; TMA = thrombotic microangiopathy.



Hemopoietic stem cell trasplantation TA-TMA

Mechanisms of ENDOTHELIAL DAMAGE

Infections

Viruses: CMV, HHV6
Adenovirus
Parvovirus B19
BK virus

Serum BK >10000 copies/mL >> TA-TMA in children with hemorrhagic cystitis (Haines HL, BBMT 2011)

Aspergillus species

Adenovirus expresses a soluble fms-like tyrosine Kinase that binds Vascular Endothelium Growth Factor (VEGF) causing TMA (Eremina V. NEnglJMed 2008, 358;11)

Hemopoietic stem cell trasplantation TA-TMA

Mechanisms of ENDOTHELIAL DAMAGE

Calcineurin and Mammalian Target of Rapamycin Inhibitors (mTor)

↓

Cyclosporine, Tacrolimus

Sirolimus, Everolimus

↓

Direct cytotoxic damage
Platelet aggregation
Elevated VWF,Thrombomodulin
Altered complement regulator proteins
Decreased production of **Nitric Oxide (NO)**

Tacrolimus + Sirolimus : ↑ TA-TMA

A phase II pilot study of tacrolimus/sirolimus GVHD prophylaxis for sibling donor hematopoietic stem cell transplantation using 3 conditioning regimens

*Roberto Rodriguez BLOOD, 4 FEBRUARY 2010 • VOLUME 115, NUMBER 5

Table 2. Diagnosis, remission status by conditioning regimen

	Flu/Mel (n = 46)	TBI/VP16 (n = 28)	Bu/Cy (n = 11)
ALL	4 (2CR, 2A)	14 (12CR, 2A)	
AML	19 (15CR, 4A)	12 (8CR, 4A)	2 (2A)
CML			5 (4CP, 1AP)
Lymphoma/CLL	14 (14A)	2 (1CR, 1A)	
MDS	2 (2A)		4 (3CR, 1A)
Multiple myeloma	3 (3A)		
Myeloproliferative disorder	4 (4CP)		

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; and CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; A, active; AP, accelerated phase; CR, complete remission; and CP, chronic phase.

overall incidence of thrombotic microangiopathy was 19%, and it was significantly higher with busulfan/cyclophosphamide (55%, $P = .005$). Tacrolimus plus sirolimus is an effective combination for acute GVHD prophylaxis and is associated with very low nonrelapse mortality. Thrombotic microangiopathy is a significant complication with this regimen, particularly in patients receiving busulfan/cyclophosphamide.

Table 4. Lung, liver, TMA toxicities, grade more than III by regimen

	Lung	P*	Liver	P*	TMA	P*
Flu/Mel (n = 46)	10 (22%)	.087	5 (11%)	.305	3 (7%)	< .005
TBI/VP16 (n = 28)	1 (4%)		5 (18%)		7 (25%)	
Bu/Cy (n = 11)	1 (9%)		3 (27%)		6 (55%)	

*Fisher exact test.

Hemopoietic stem cell trasplantation TA-TMA

Mechanisms of ENDOTHELIAL DAMAGE

Calcineurin and Mammalian Target of Rapamycin Inhibitors (mTor)

↓

Cyclosporine, Tacrolimus

Sirolimus, Everolimus

↓

Direct cytotoxic damage
Platelet aggregation
Elevated VWF,Thrombomodulin
Altered complement regulator proteins
Decreased production of **Nitric Oxide (NO)**

Tacrolimus + Sirolimus : ↑ TA-TMA

Sirolimus: ↑ TA-TMA
- prevents repair of injured renal endothelium;
- decreases renal **VEGF** production.

VEGF Inhibition and Renal Thrombotic Microangiopathy

Vera Eremina, N ENGL J MED MARCH 13, 2008

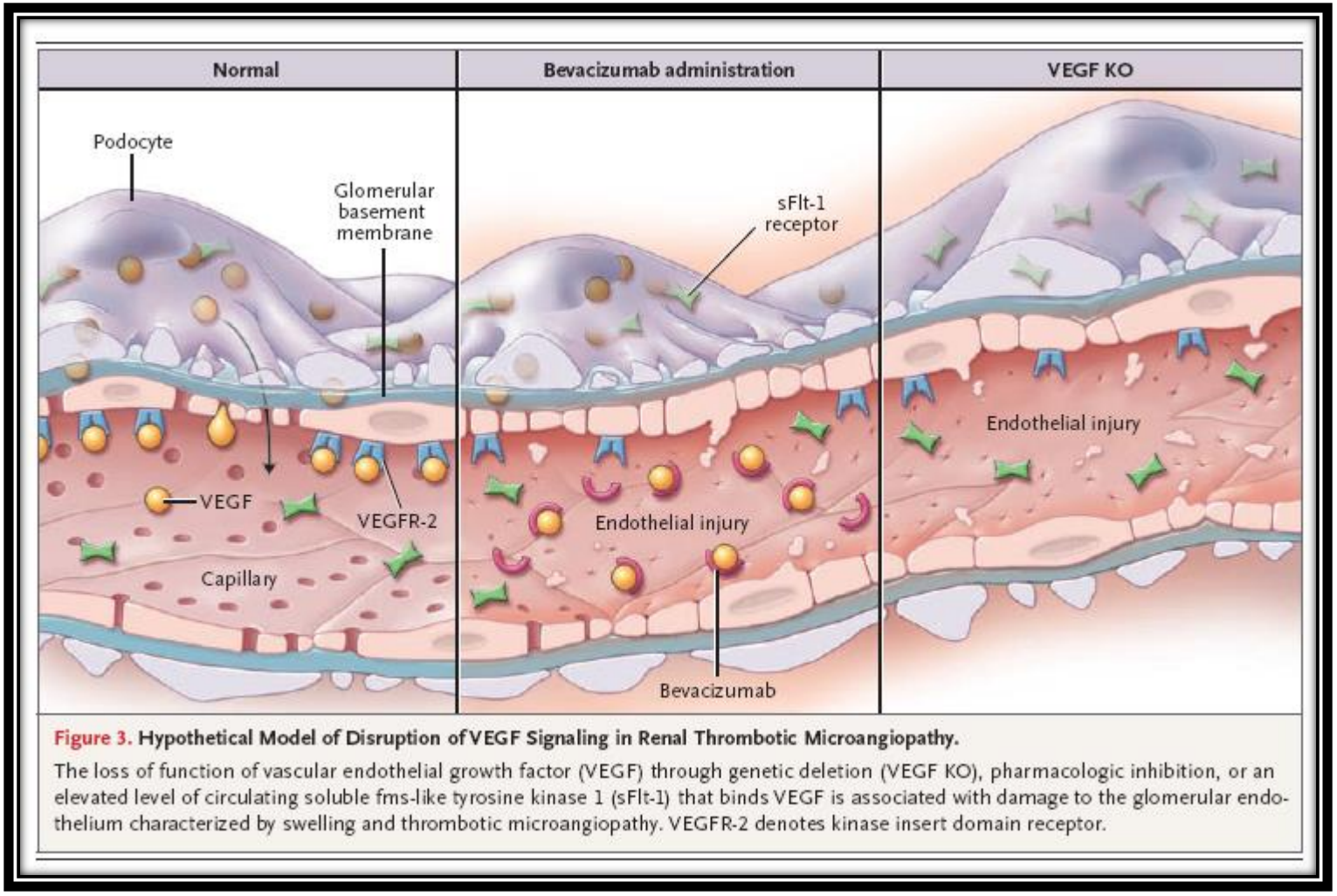


Figure 3. Hypothetical Model of Disruption of VEGF Signaling in Renal Thrombotic Microangiopathy.

The loss of function of vascular endothelial growth factor (VEGF) through genetic deletion (VEGF KO), pharmacologic inhibition, or an elevated level of circulating soluble fms-like tyrosine kinase 1 (sFlt-1) that binds VEGF is associated with damage to the glomerular endothelium characterized by swelling and thrombotic microangiopathy. VEGFR-2 denotes kinase insert domain receptor.

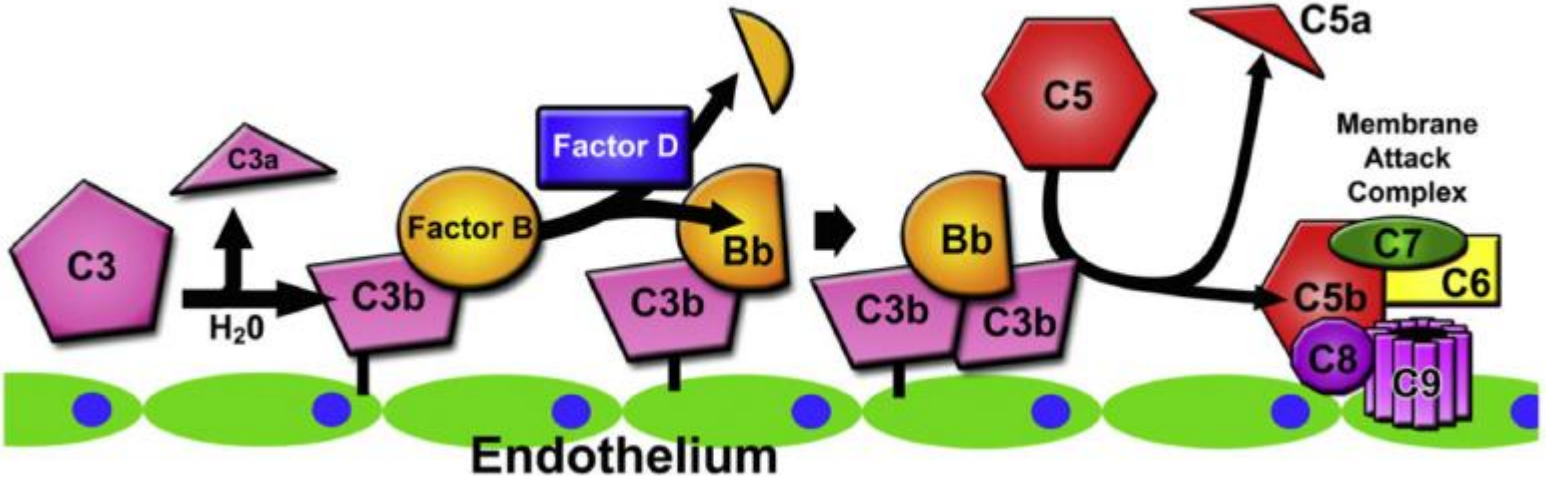
Hemopoietic stem cell trasplantation TA-TMA

Mechanisms of ENDOTHELIAL DAMAGE

Complement

Role well-established in the pathogenesis of aHUS

Defects in one/more regulatory proteins of the alternative pathway



Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy

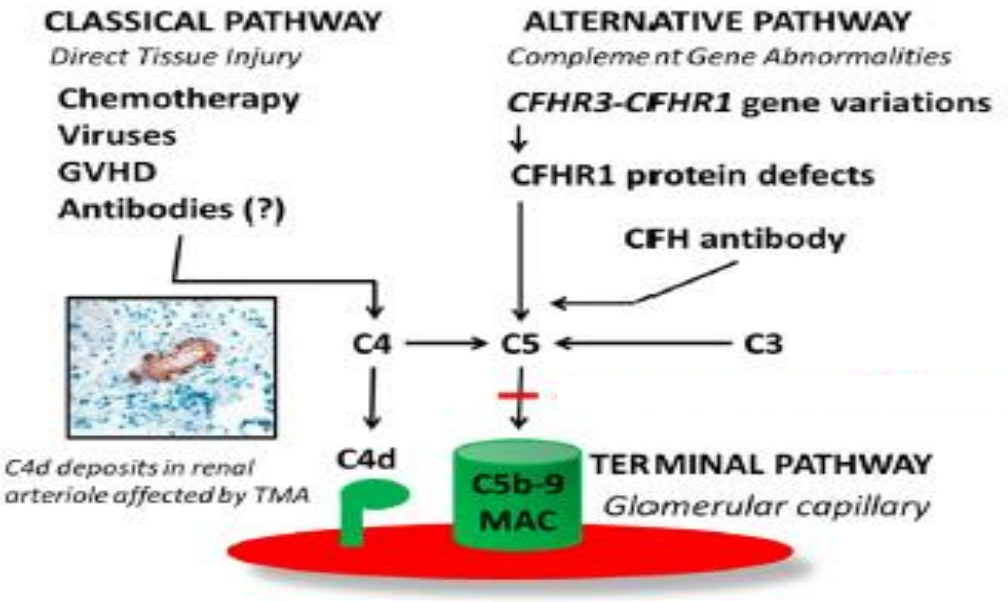
BLOOD, 19 SEPTEMBER 2013 • VOLUME 122, NUMBER 12

Sonata Jodele,[1] Christoph Licht,[2] Jens Goebel,[3] Bradley P. Dixon,[3] Kejian Zhang,[4] Theru A. Sivakumaran,[4] Stella M. Davies,[1] Fred G. Pluthero,[2] Lily Lu,[2] and Benjamin L. Laskin[5]

Table 2. Complement system analysis in patients with HSCT-TMA

Patient	Transplant type	*CFI,CFH,MCP,CFB,CFR5* (direct sequence analysis)	Recipient *CFH-CFHR5* (MLPA)	Donor *CFH-CFHR5* (MLPA)	CFH antibody (ELISA)	CFHR1 protein analysis (western blot)
1	autologous	normal alleles	**del(CFHR3-CFHR1)*	n/a	absent	present
2	autologous	normal alleles	**del(CFHR3-CFHR1)*	n/a	absent	present
3	autologous	normal alleles	**del(CFHR1-CFHR4)*	n/a	absent	present
4	allogeneic	normal alleles	**del(CFHR3-CFHR1)*	normal allele	present	present
5	allogeneic	normal alleles	**del(CFHR3-CFHR1)*	**del(CFHR3-CFHR1)*	present	present
6	allogeneic	normal alleles	normal allele	normal allele	present	present

CFR, complement factor H-related gene 5.
**del* refers to heterozygous deletions.



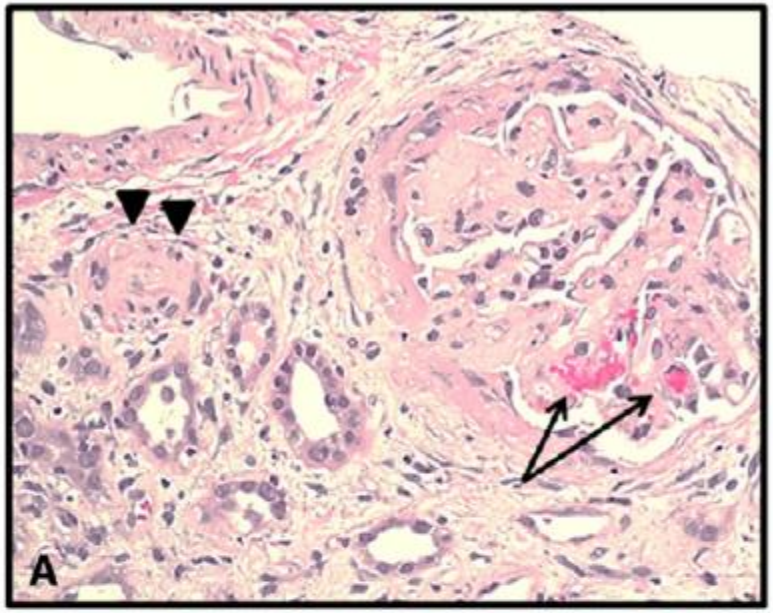
Hemopoietic stem cell trasplantation TA-TMA

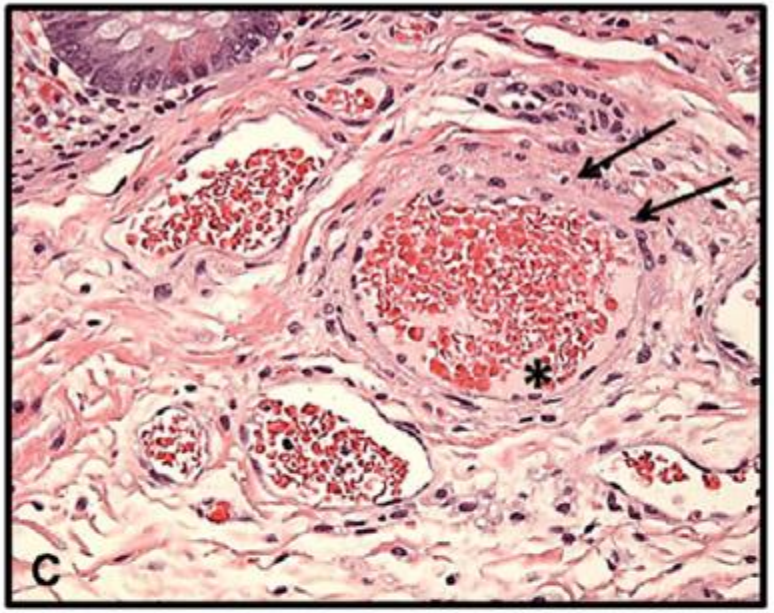
Relative renal tissue specificity of TA-TMA

- Fenestrated endothelium of the glomerulus;
- Differential expression of proteins regulating coagulation cascade;
- More turbolent blood flow through the renal microvascolature.

Multivisceral endothelial damage in TA-TMA

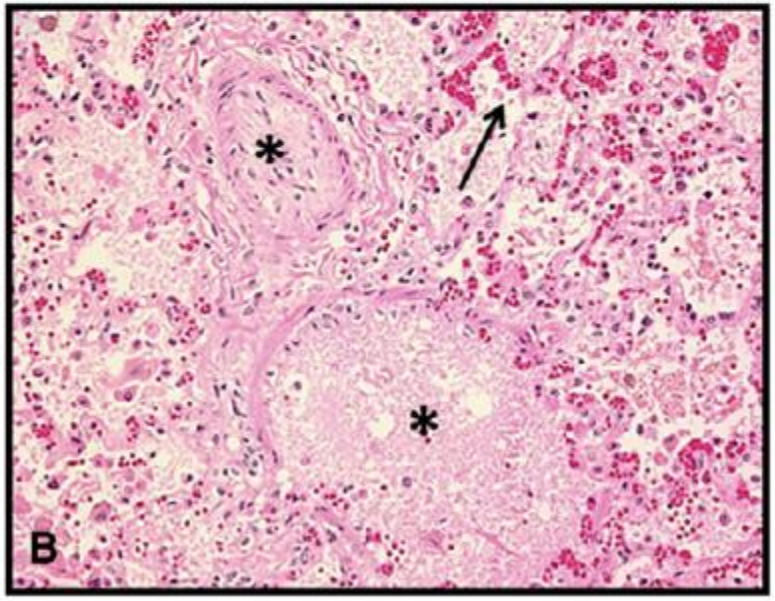
Kidney

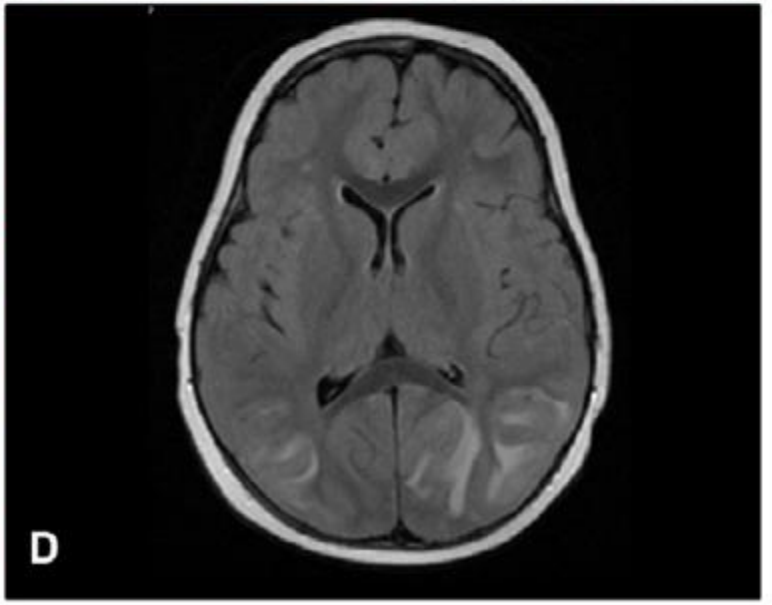




Small bowel

Lung





Brain

Clinicopathological manifestations and treatment of intestinal transplant-associated microangiopathy

Y Inamoto[1,2], M Ito[3], R Suzuki[4], T Nishida[1,2], H Iida[5], A Kohno[6], M Sawa[7], M Murata[2], S Nishiwaki[1], T Oba[1], M Yanada[2], T Naoe[2], R Ichihashi[6], M Fujino[3], T Yamaguchi[3], Y Morishita[6], N Hirabayashi[3], Y Kodera[1] and K Miyamura[1], for the Nagoya Blood and Marrow Transplantation Group

Bone Marrow Transplantation (2009) 44, 43–49

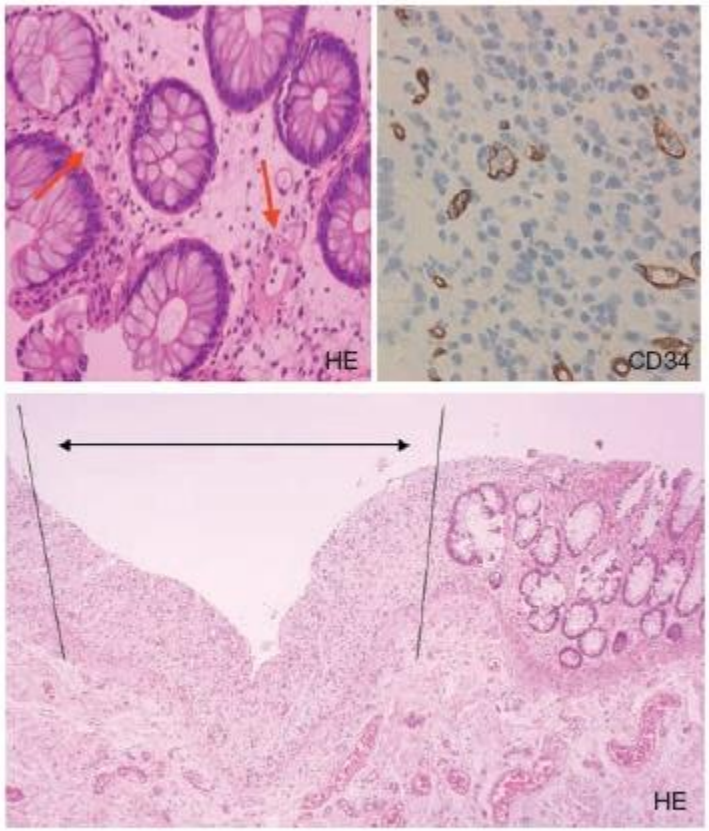


Figure 1 Colonoscopic histopathological findings. Microangiopathy with crypt loss in i-TAM (red arrow). CD34 immunostaining is helpful. Wedge-shaped segmental injury (black arrow). i-TAM, intestinal transplant-associated microangiopathy.

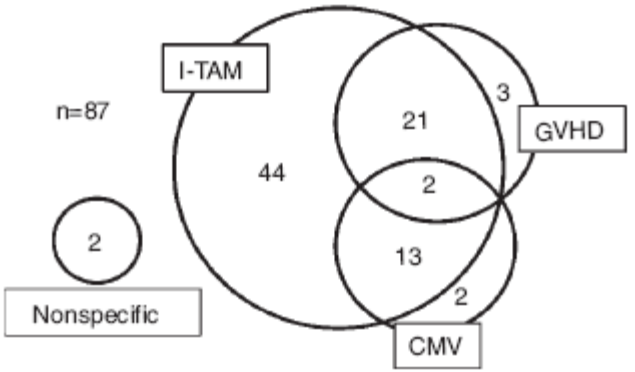


Figure 2 The number of patients with each histopathological diagnosis. i-TAM, intestinal transplant-associated microangiopathy.

Table 2 Histopathological findings of i-TAM

	Incidence (%)
Microangiopathy with crypt loss	80 (100)
Interstitial edema with hemorrhage with or without fragmented RBCs	31 (39)
Crypt degeneration with detachment and/or apoptotic epithelial cells	74 (93)
Residual neuroendocrine cells	34 (43)
Plt thrombi	24 (30)

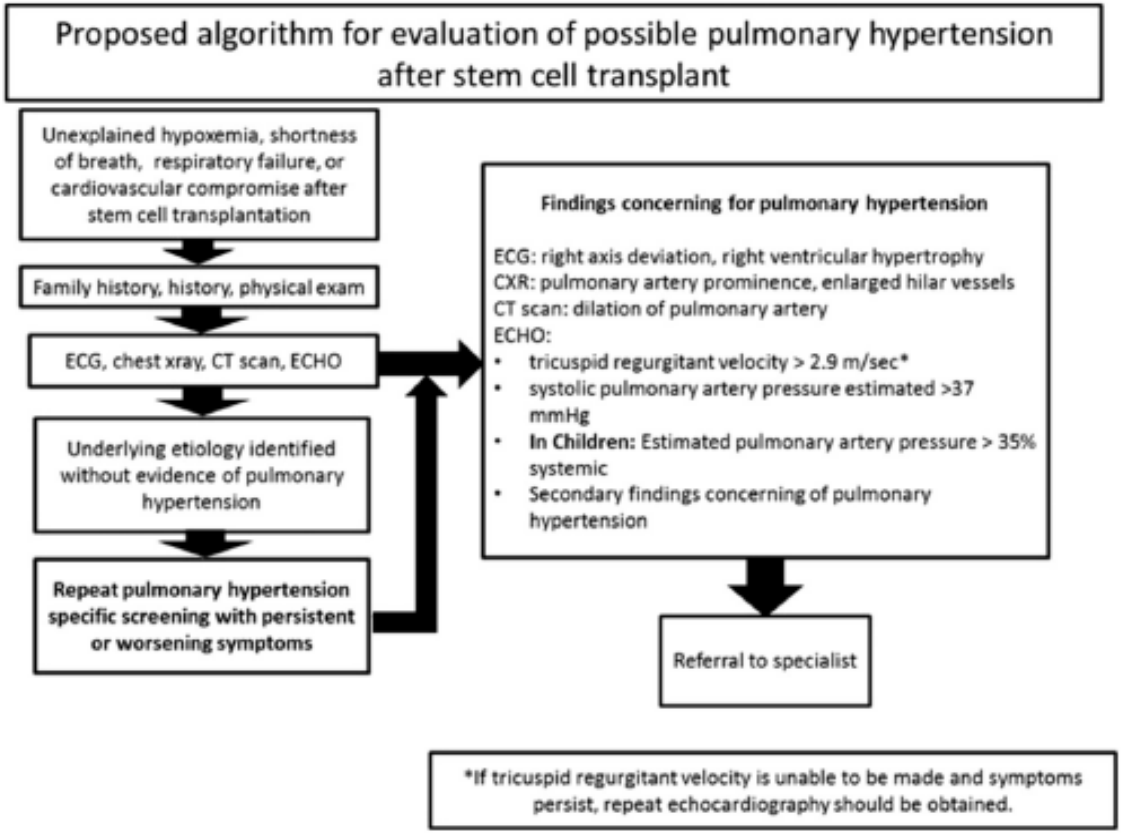
Abbreviation: i-TAM = intestinal transplant-associated microangiopathy.

Table 3 Affected sites of intestine

	Incidence (%)
Sites	
Terminal ileum	90
Ascending colon	79
Transverse colon	83
Descending colon	77
Sigmoid colon	73
Rectum	73
Affected pattern	
Regional/diffuse	33%/67%

HSCT patients with pulmonary TA-TMA

Pulmonary Hypertension
presenting with unexplained hypoxemia



Multivisceral endothelial damage in TA-TMA

POLYSIEROSITIS

Refractory pericardial effusion

Pleural effusion

Ascites

Often without generalized edema

Often without signs of GvHD

Table 1. Demographic and transplant characteristics of pediatric patients with transplant-associated TMA ($n = 33$)

	HSCT patients with TMA and PEFs (n = 15)	*HSCT patients with TMA and without PEFs (n = 18)*	P-*value*[a]
Sex			
Male ($n = 21$)	8 (53%)	13 (72%)	0.300
Diagnosis			
BM failure ($n = 14$)	5 (33%)	9 (50%)	0.482
Immunodeficiency ($n = 14$)	8 (53%)	6 (33%)	0.304
Malignancy ($n = 4$)	2 (14%)	2 (11%)	1.000
Genetic or metabolic disorder ($n = 1$)	0 (0%)	1 (6%)	1.000
Stem cell source			
Marrow ($n = 22$)	10 (67%)	12 (67%)	1.000
Cord blood ($n = 1$)	1 (7%)	0 (0%)	0.454
PBSC ($n = 10$)	4 (26%)	6 (33%)	0.722
Donor			
Unrelated donor ($n = 25$)	13 (87%)	12 (67%)	0.242
Matched sibling donor ($n = 8$)	2 (13%)	6 (33%)	
Conditioning regimen			
Myeloablative ($n = 16$)	6 (40%)	10 (56%)	0.491
Reduced intensity ($n = 17$)	9 (60%)	8 (44%)	

Abbreviations: HSCT = hematopoietic SCT; PEF = pericardial effusion; TMA = thrombotic microangiopathy. [a]*P*-values obtained with Fisher's exact test.

Lerner D, BMT 2014

Hemopoietic stem cell trasplantation TA-TMA

Diagnostic criteria

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[89]	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 × 10⁹/L or a ≥ 50% decrease in platelet count	Thrombocytopenia: < 50 × 10⁹/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

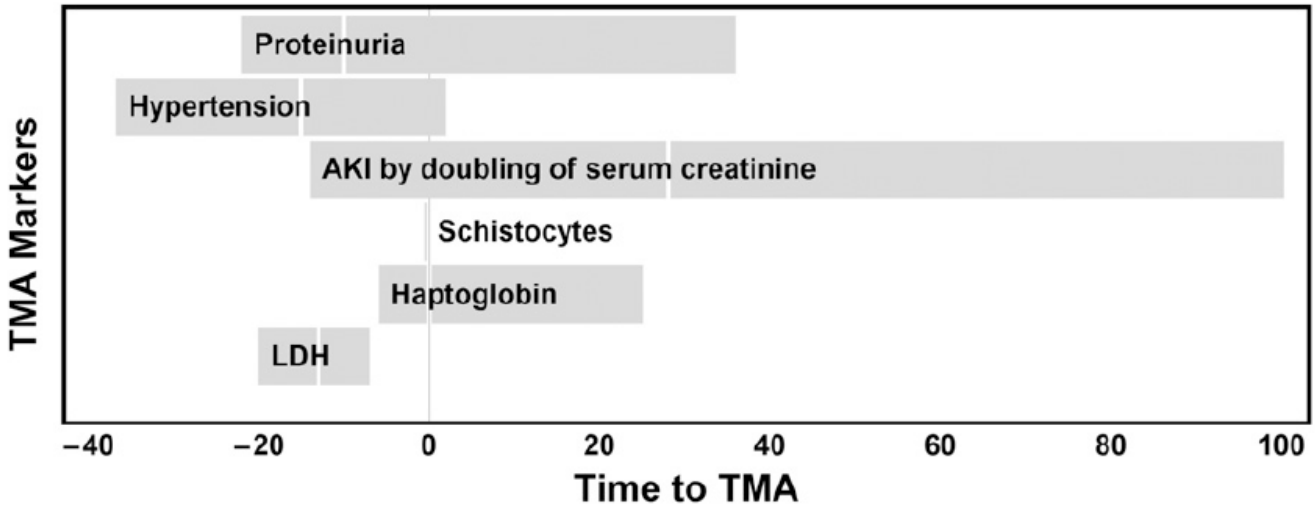
Reprinted by permission from Wolters Kluwer Health.[53]

Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults

Sonata Jodele, BLOOD, 24 JULY 2014 • VOLUME 124, NUMBER 4

Table 2. Laboratory markers, clinical risk factors, and complications

Ninety allogeneic recipients	Subjects with TMA (n = 39)	Subjects without TMA (n = 51)	*P* value
Proteinuria ≥30 mg/dL	26 (66.7%)	16 (31.4%)	<.01
Subjects with elevated sC5b-9	26/39 (67%)	4/20 (20%)	<.01
Number of medications to control hypertension‡	3 [2-4.5]	2 [1-3]	<.01



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.

Patients "**2+7**" have 84% NRM at 1 year post HSCT

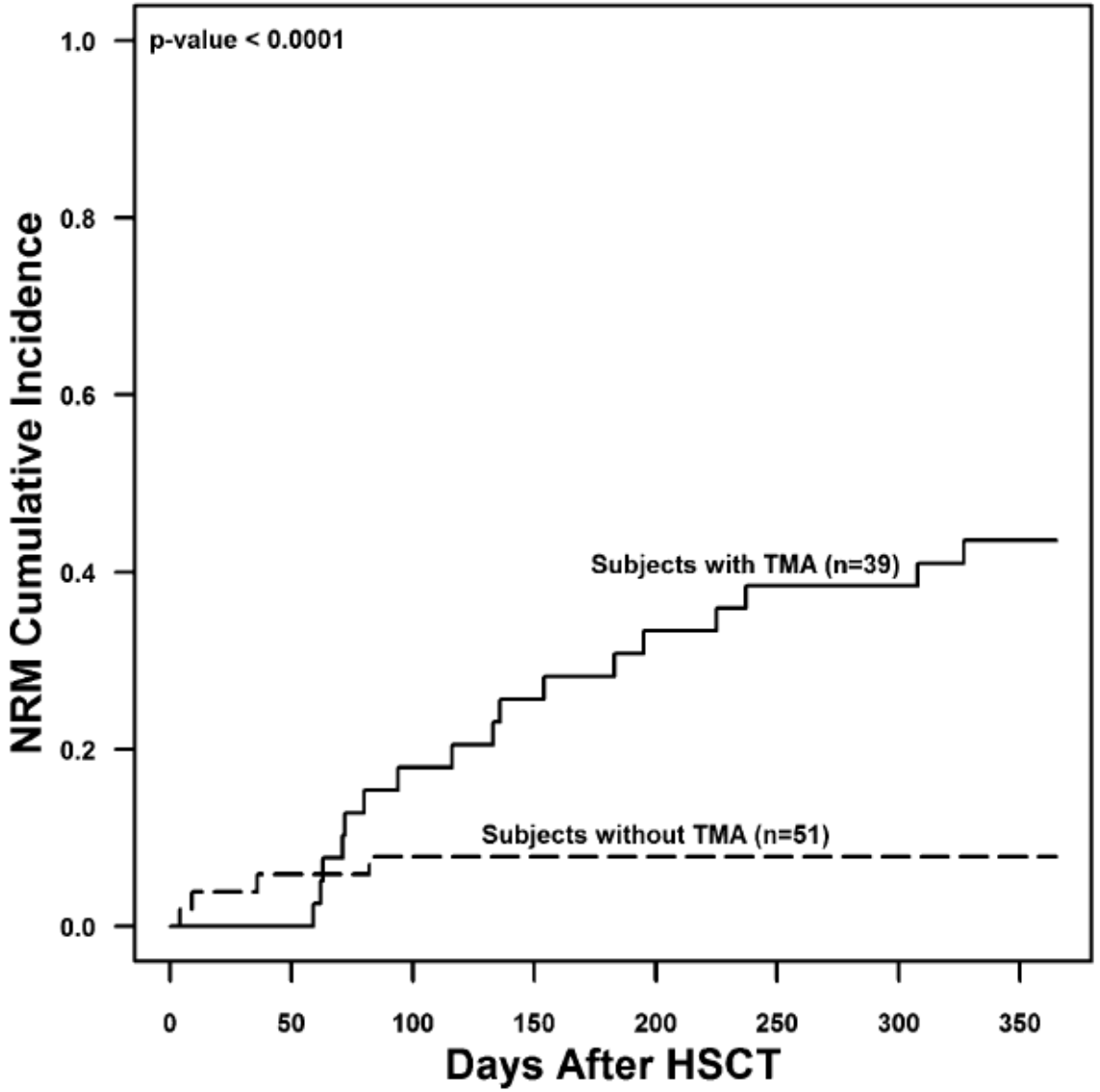
All the others with TA-TMA recovered and survived

Sonata Jodele[a]

Blood Rev. 2015 May ; 29(3): 191–204

Hemopoietic stem cell trasplantation TA-TMA

Prognosis



Hemopoietic stem cell trasplantation TA-TMA

Prognosis

Kidney dysfunction remains a significant complication in HSCT pts:

- Up to 8% pts require acute renal replacement therapy → 6-fold increased odds of death and a mortality rate>80%;
- In those surviving an **acute renal insult (AKI),** developing **chronic kidney disease (CKD)** markedly increases the risk of cardiovascular disease because of accelerated atherosclerosis from endothelial damage and concomitant hypertension;
- HSCT pts progressed to CKD are 16 times more likely to develop end-stage renal disease (ESRD);
- HSCT pts needing chronic dialysis have mortality rates of 90%, much higher than other pts with ESRD.

TA-TMA causes an even higher risk of AKI, CKD and the need for long term dialysis, increasing morbidity and mortality

Acute renal failure after allogeneic myeloablative stem cell transplantation: retrospective analysis of incidence, risk factors and survival

S Kersting Bone Marrow Transplantation (2007) 39, 359–365

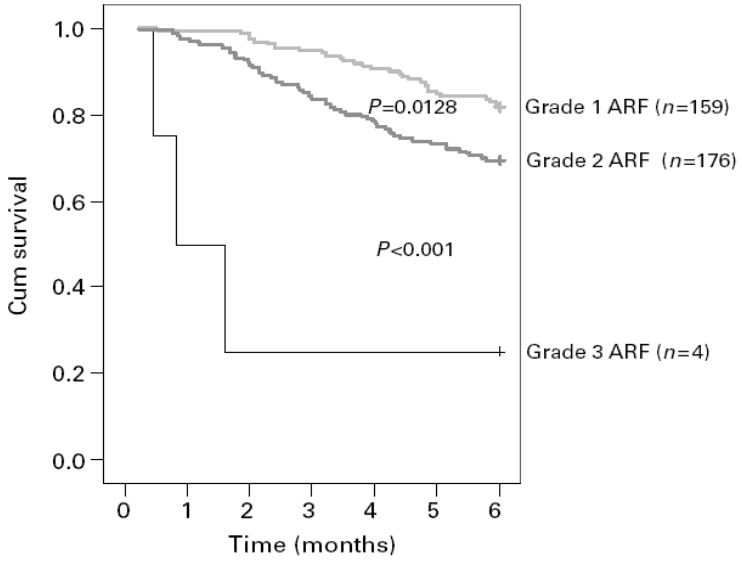


Figure 2 Survival in patients with ARF.

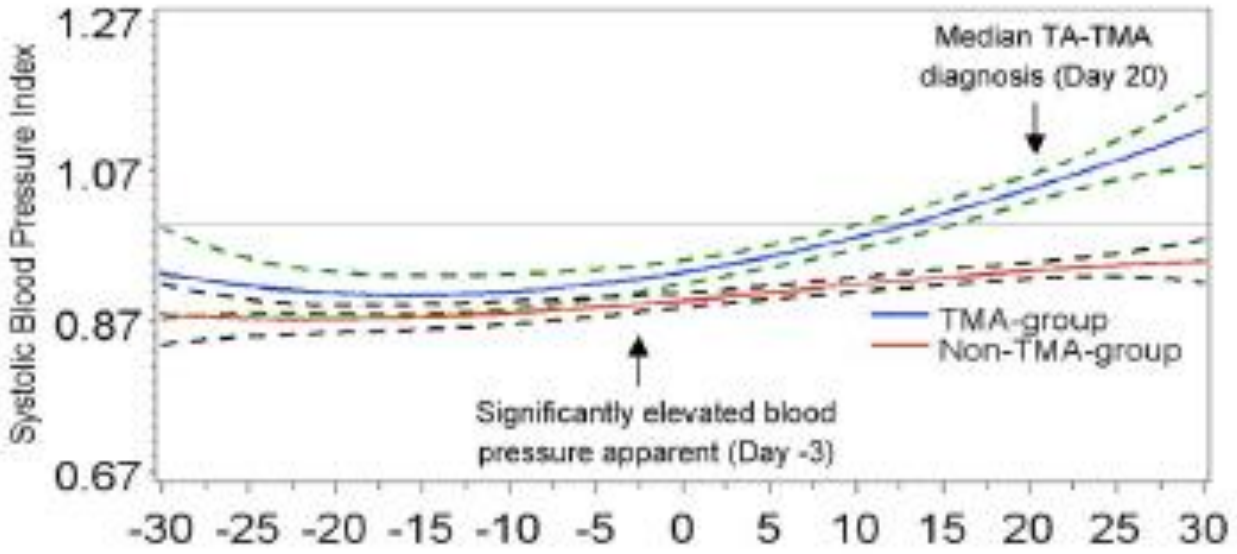
Table 3 Post-transplantation complications, cyclosporine trough levels and mortality data

	All patients	*ARF grade 2–3*	*No ARF*	P-*value*
Number of patients	363 (100%)	180 (49.6%)	183 (50.4%)	
Complications[a]				$P<0.001$
Yes	98 (27%)	64 (65.3%)	34 (34.7%)	
No	265 (73%)	116 (43.8%)	149 (56.2%)	
Acute GVHD				NS
No-Grade1	209 (57.6%)	106 (50.7%)	103 (49.3%)	
Grade II	137 (37.7%)	65 (47.4%)	72 (52.6%)	
Grade III–IV	17 (4.7%)	9 (52.9%)	8 (47.1%)	
SOS				NS
Yes	16 (4.4%)	11 (68.8%)	5 (31.2%)	
No	347 (95.6%)	169 (48.7%)	178 (51.3%)	
TTP				$P=0.017$
Yes	12 (3.3%)	10 (83.3%)	2 (16.7%)	
No	351 (96.7%)	170 (48.4%)	181 (51.6%)	
ICU				$P<0.001$
Yes	16 (4.4%)	15 (93.8%)	1 (6.2%)	
No	347 (95.6%)	165 (47.6%)	182 (52.4%)	

Hemopoietic stem cell trasplantation TA-TMA

Treatment (1)

Supportive :



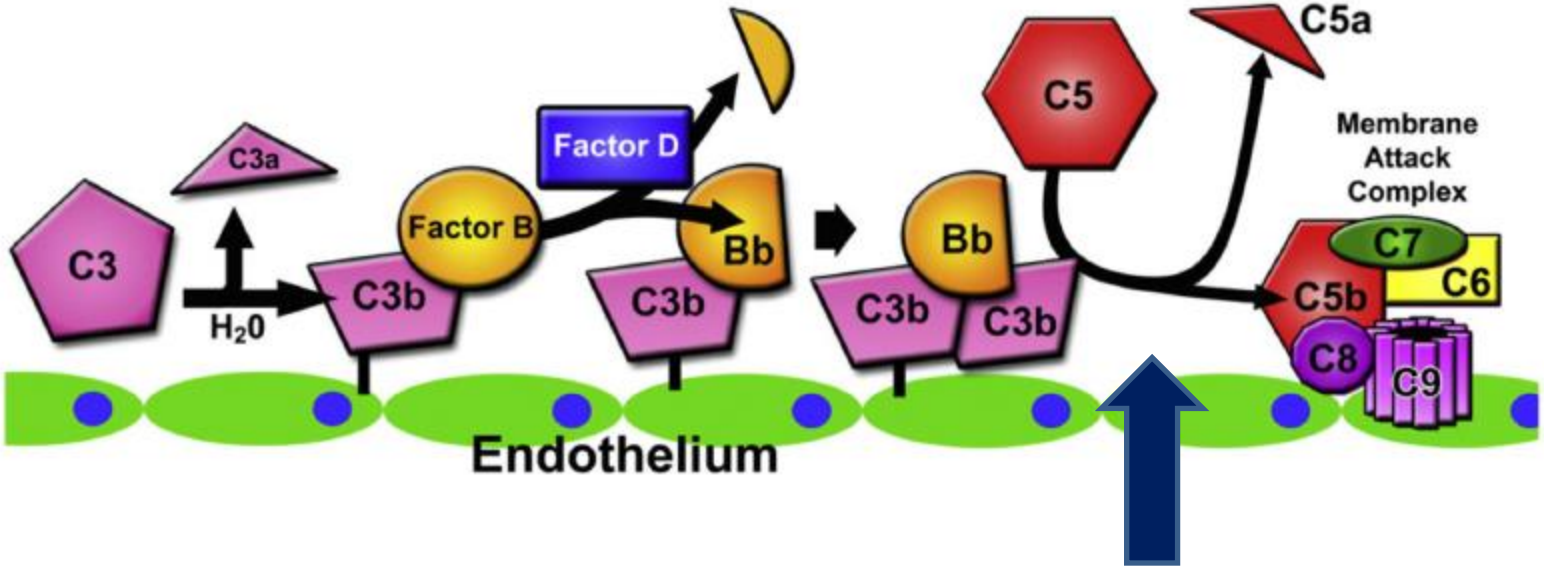
Hemopoietic stem cell trasplantation TA-TMA

Treatment (1)

Disease targeted:

- Eculizumab
- TPE
- Rituximab
- Defibrotide

ECULIZUMAB



Complement blockade agent

ECULIZUMAB

- **Complement blockade agent**;

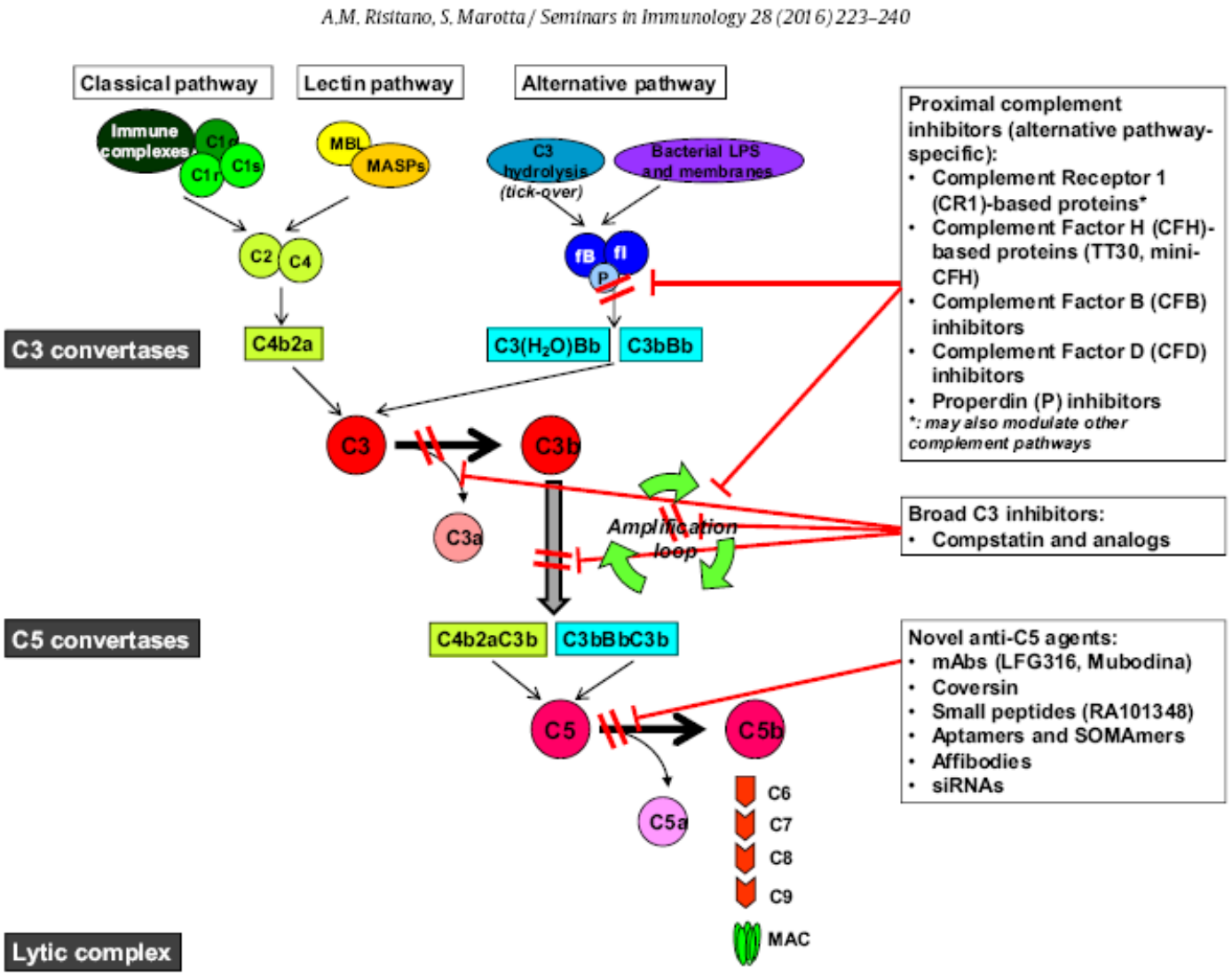
- **Good results**: 12 TA-TMA treated → 50% hematological response, 33% overall survival (*de Fontbrune , Transplantation 2015*);

  18 pediatric pts → 61% response rate, 56% overall survival (*Jodele S, BBMT 2016*);

- **Challenges**: difficulty in achieving therapeutic levels in HSCT pts;
  higher doses/more frequent infusions in children;
  limited availability in certain countries;
  significant cost;
  longer therapy than aHUS pts;
  no concomitant use of TPE → drug removing;
  of Rituximab → decrease activity;

- **On label therapy in aHUS**.

Novel anti-complement agents



Therapeutic plasma exchange (TPE)

Variable outcome in retrospective reviews
Lack of controlled prospective trials

BMT consensus guidelines on TA-TMA (1991-2003):

- poor responses (median response rate 36,5%);
- high mortality rates (80% in most severe cases).

More recent data (2003-2011):
Better median response rate (59%) in uncontrolled and heterogeneous pts

Therapeutic plasma exchange (TPE)

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

P-TMA indicates probable TA-TMA (see Table 1); and D-TMA, definite TA-TMA.

Therapeutic plasma exchange (TPE)

USEFUL in selected patients:

- HSCT pts with documented Factor H Ab

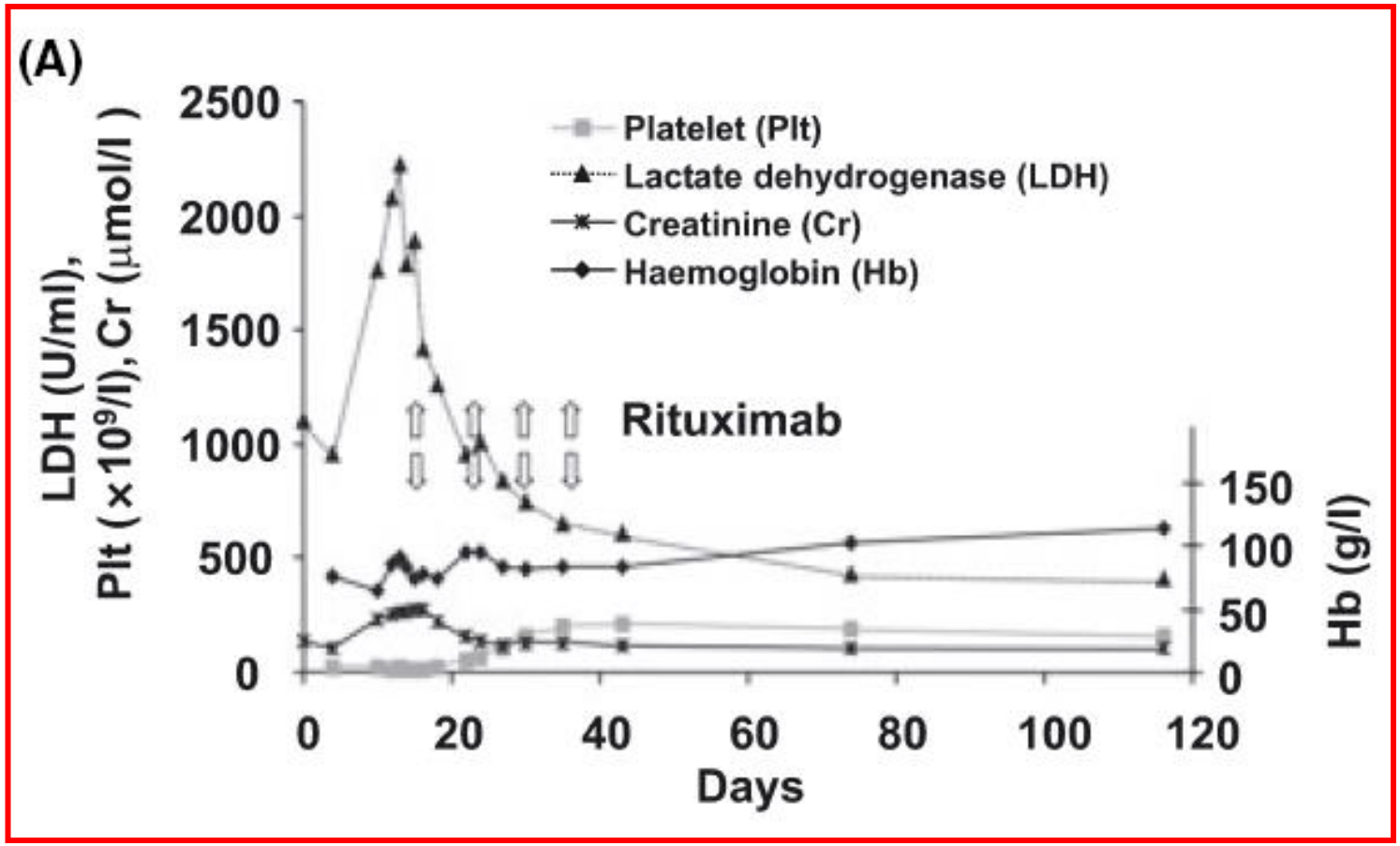
- Initial therapy in very ill pts where other treatment options are absent.

RITUXIMAB (anti CD20 monoclonal antibody)

- Possible effects of Ab depletion and immune regulation in HSCT
- Benefit in pts with C4d deposition in the kidney arterioles and in pts with complement Factor H autoAb;
- Schedule: 375 mg/m2 /dose IV weekly; if used with TPE, administer immediately after TPE to obtain maximum efficacy;
- On label : TTP refractory/relapsed after TPE.

Successful treatment of thrombotic microangiopathy after haematopoietic stem cell transplantation with rituximab

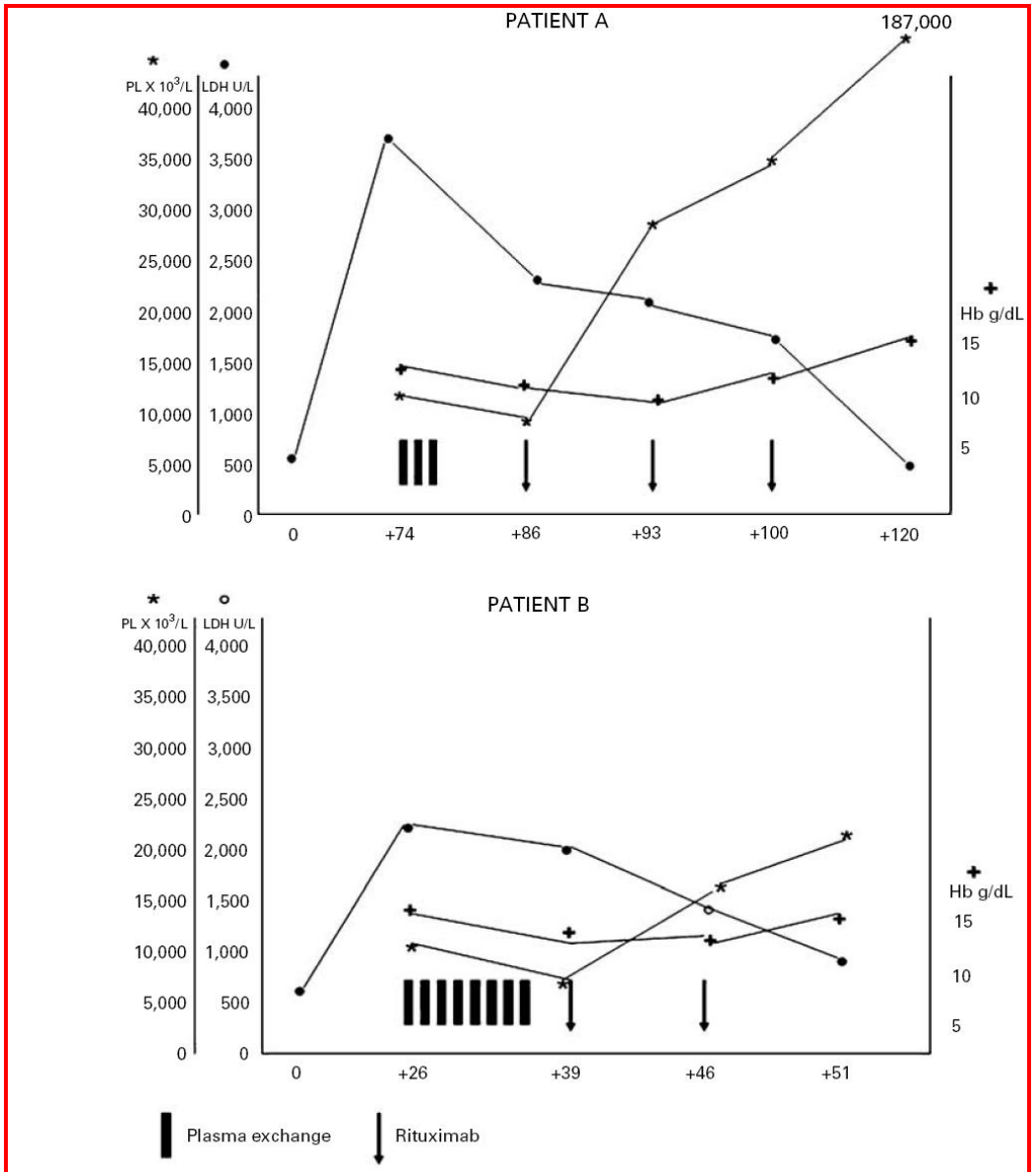
Wing-Yan Au, BrJHematol;2007, 137: 475-78



Four of five postHSCT cases remitted with Rituximab

Rituximab for allo-SCT-associated thrombotic thrombocytopenic purpura

AM Carella, *Bone Marrow Transplantation* (2008) **41,** 1063–1065;



Plt, Hb and lactate dehydrogenase (LDH) changes in two patients with SCT-associated TTP treated with rituximab.

DEFIBROTIDE

Biological properties of defibrotide

- The major effects of defibrotide are:
  - **Reducing inflammation**[1] by decreasing local cytokine release[1]
  - **Inhibiting thrombosis** by decreasing levels of tissue thromboplastin and increasing TFPI[1]
  - **Inducing fibrinolysis** by increasing levels of tPA and by reducing PAI-1 levels, which have been demonstrated to play a key role in VOD[1–4]
  - **Blocking TF expression**, the most important activator of the coagulation cascade which may help reduce microvascular fibrin deposition[1,3,4]
  - **Modulating platelet activity** by increasing levels of endogenous prostaglandins (PGI-2 and E-2)[1–3]

Defibrotide protects and stabilises endothelium without enhancing systemic bleeding[1]

TFPI, tissue factor pathway inhibitor;
PAI-1, plasminogen activator inhibitor 1; TF, tissue factor

1. Morabito F et al. *Expert Opin Biol Ther* 2009;9:763–772
2. Cocchani S & Biagi G. *Cardiovasc Drug Rev* 1991;9:172–196;
3. Palmer KJ & Goa KL. *Drugs* 1993;45:259–294;
4. Falanga A et al. *Leukemia* 2003;17:1636–1642

DEFIBROTIDE

- Used in hepatic VOD with a 30-60% complete response rate (*Choi CM,Drugs 2009*)
- Useful to prevent aGvHD grades II-IV in HSCT pts prophylaxed for VOD (*Corbacioglu S, Lancet 2012*)
- Protective effect on the endothelium damaged by ciclosporine, tacrolimus, Tacrolimus+sirolimus (*Carmona A, BBMT 2013*)

Use in TA-TMA mostly in Europe, same schedule as in VOD → 6, 25 mg/kg/dose iv every 6 hours

Off-label therapy

Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation

P Corti[1]

Bone Marrow Transplantation (2002) **29,** 542–543.

Table 1 Patients, TTP characteristics and outcome

Patients	*Sex*	*Age years*	*Diagnosis at BMT*	*BMT type*	*TTP index*	*LDH max*[a]	*TTP grade*	*Symptoms*	*DFT therapy (days)*	*No. of plasma phereses*	*Outcome*		*Cause of death*
											TTP	*Patients*	
1	M	3	AML (1st CR)	Rel	<20	2t	mild	—	17	—	TR	alive	—
2	M	1	FEL	Unrel	>20	3t	severe	SHS	51	—	TR	alive	—
3	M	12	ALL (2nd CR)	Rel	>20	2t	severe	SHS	98	—	TR	alive	—
4	F	7	ALL (3rd CR)	Unrel	>20	5t	severe	SHS	61	—	TR[b]	alive	—
5	F	35	CML (1st CP)	Unrel	>20	7t	severe	CNS	23	2	NR	dead	PC
6	F	16	ALL (3rd CR)	Unrel	>20	2t	severe	—	46	2	PR	dead	PD
7	M	33	HL (PD)	Rel	>20	2t	severe	K,SHS	30	—	TR	alive	—
8	M	20	ALL (3rd CR)	Unrel	>20	2t	severe	CNS, SHS	17	3	NR	dead	IP
9	M	35	ALL (2nd CR)	Unrel	>20	5t	severe	—	34	—	PR	dead	PG
10	F	37	AML (1st CR)	Rel	<20	2t	mild	—	38	—	TR	alive	—
11	F	55	CML (1st CP)	Rel	>20	1t	severe	SHS	64	2	NR	dead	GG
12	F	30	AML (PD)	Unrel	>20	2t	severe	SHS	41	3	PR	dead	IP

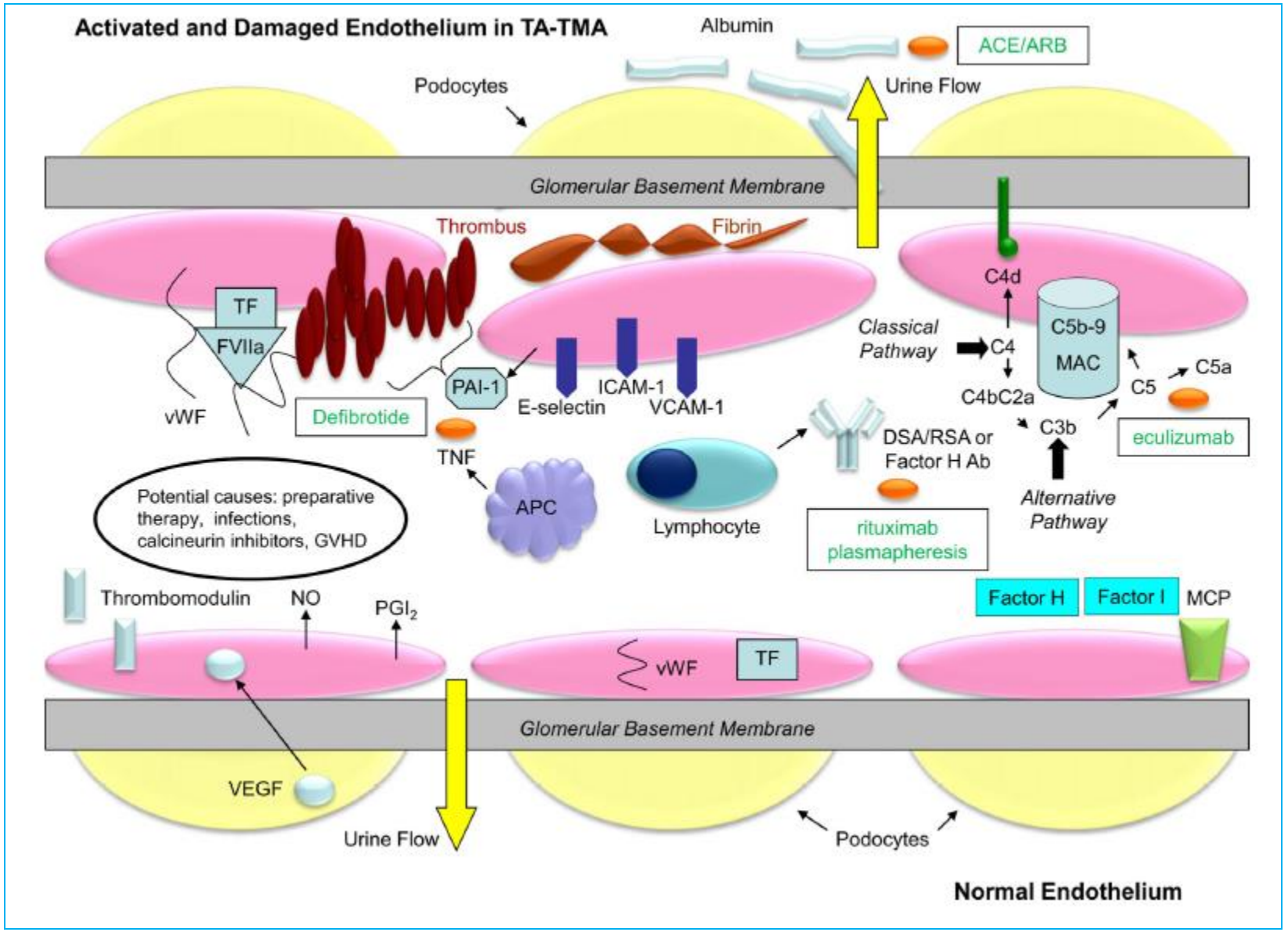
[a]Expressed as a multiple (times) of the normal level (range 150–300 IU/l).
[b]This case showed a total response within 3 months.
AML = acute myeloid leukemia; FEL = familiar lymphohistiocytosis; ALL = acute lymphoblastic leukemia; CML = chronic myeloid leukemia; HL = Hodgkin's lymphoma; CR = complete remission; CP = chronic phase; PD = presence of disease; Rel = related BMT; Unrel = unrelated BMT; SHS = severe hemorrhagic symptoms; K = kidney involvement; CNS = central nervous system involvement; TR = total response; PR = partial response; NR = no response; PC = pulmonary candidiasis; PD = progression of disease; IP = interstitial pneumonia; PG = pulmonary GVHD; GG = gastroenteric GVHD.

6/12 Complete Response

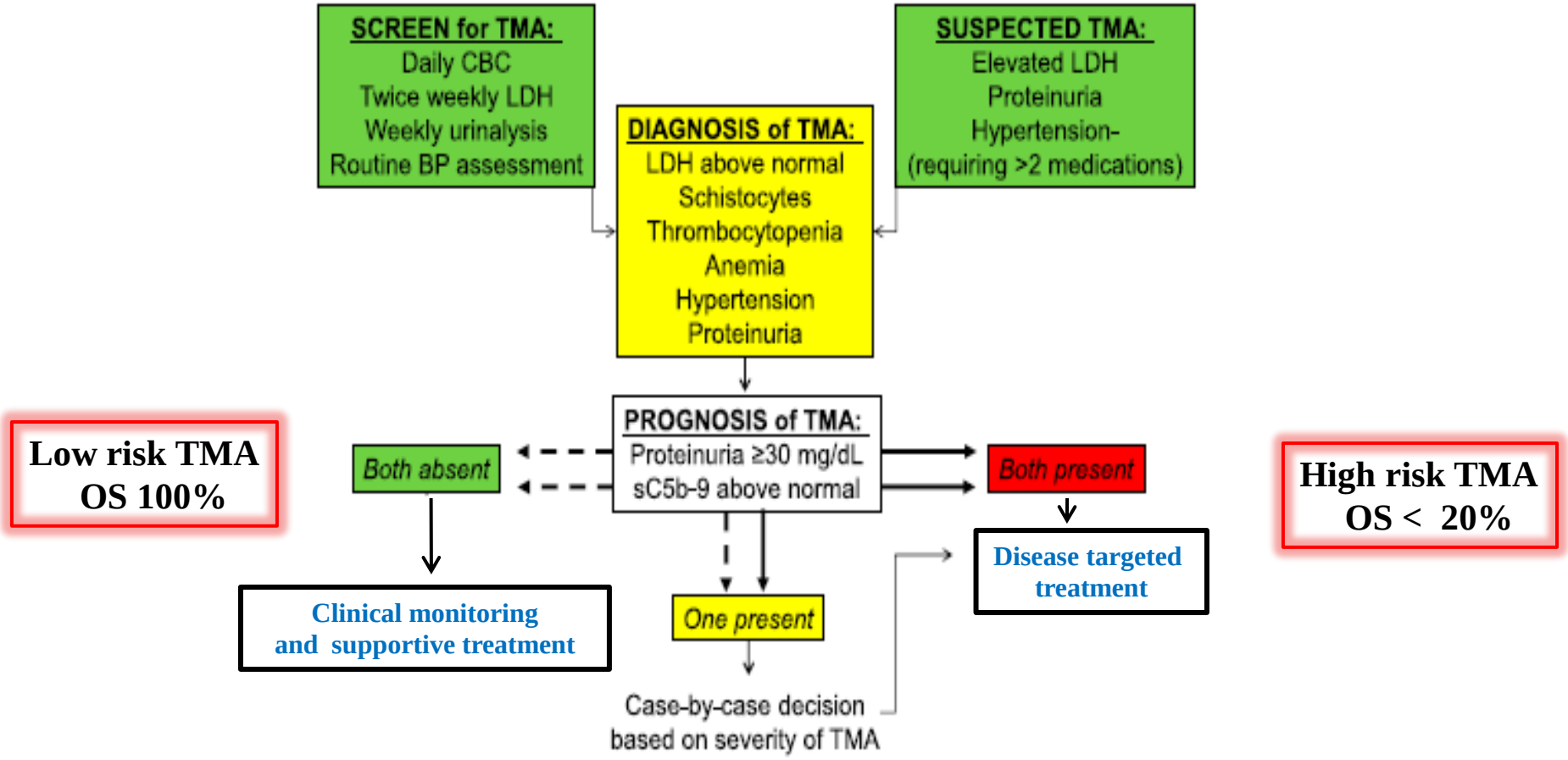
3/12 Partial Response

5/12 TPE + Defibrotide

Molecular pathogenesis and potential treatments for thrombotic microangiopathy in the glomerular endothelium



Algorithm for the evaluation of TMA after HSCT



Hemopoietic stem cell trasplantation TA-TMA

Mechanisms of ENDOTHELIAL DAMAGE

Graft versus Host Disease (GvHD)
Cytokines

During engraftement, donor T lymphocytes first encounter host endothelial cells;

Donor T cells produce cytokines (IL-8,IL-12, Thrombomodulin) that cause host endothelium cells apoptosis and lysis mediated by Perforin, Granzyme B, TNF

Against are:

- Increase immunosuppression doesn't prevent/treat TMA;
- Stop Immunosuppression often decreases TMA;
- Renal pathology in GvHD biopsies is different from TMA renal biopsies

Could TA-TMA be a form of renal or endothelium GvHD ?

Hemopoietic stem cell trasplantation TA-TMA

Mechanisms of ENDOTHELIAL DAMAGE

Coagulation cascade
Endothelial markers

All the coagulation cascade, being regulated by the endothelium, contributes to the development of TA-TMA

PAI-1 is increased in various endothelial disfunction states
Heparin cofactor II is increased in pre HSCT phase in pts who develop TMA

Circulating endothelial cells (CECs) are a marker and a mechanism of endothelial damage.

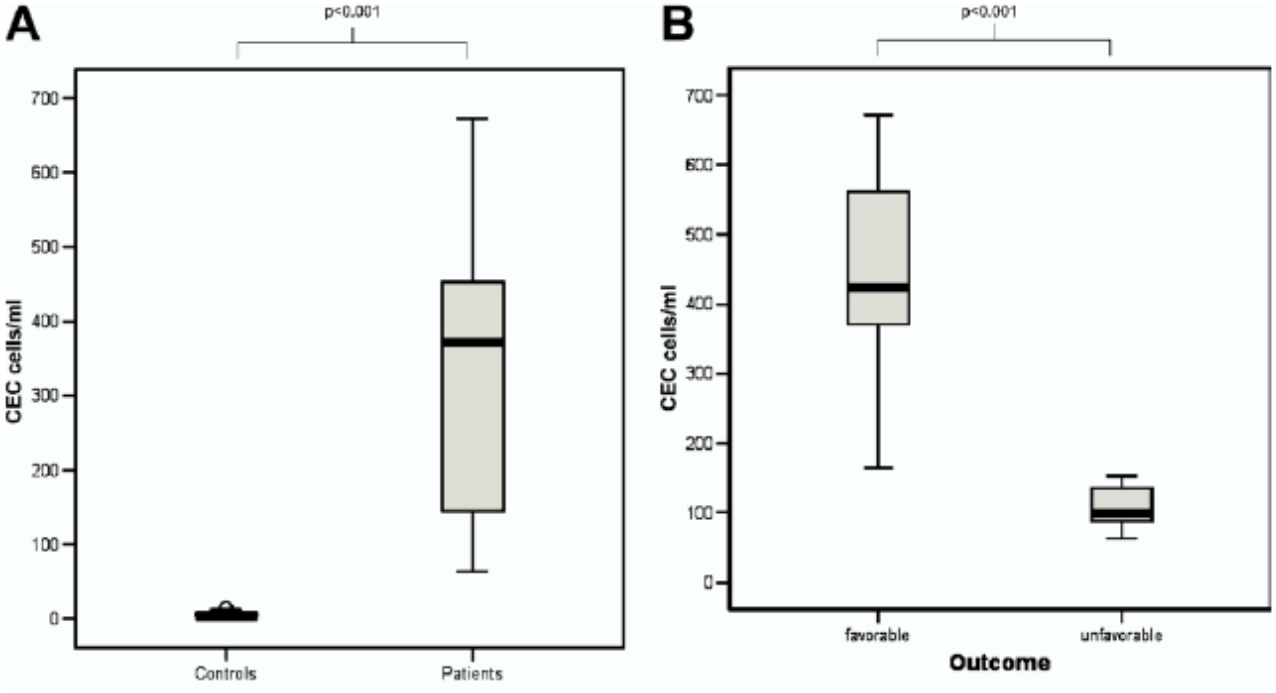
Circulating Endothelial Cells as a Prognostic Marker in Thrombotic Microangiopathy

Uta Erdbruegger, *American Journal of Kidney Diseases*, Vol 48, No 4 (October), 2006: pp 564-570

Table 1. Patient Characteristics

Patient No.	Sex	Age (y)	Cause of TMA	Outcome	vWFcP	Creatinine at Discharge (mg/dL)
1	F	34	BMT (B-NHL), TMA: 5 mo after aPBSCT	Clinically improved	Normal	0.83*
2	M	34	BMT (ALL), TMA: 18 d after aPBSCT	Clinically improved	Normal	0.97*
3	M	38	Decreased vWFcP activity	Clinically improved	25% w/o CI	0.81*
4	M	62	Decreased vWFcP activity & circulating inhibitor	Clinically improved	5% with CI	0.84*
5	M	46	Decreased vWFcP activity & circulating inhibitor	Clinically improved	3% with CI	0.70*
6	F	51	Decreased vWFcP activity	Clinically improved	25% w/o CI	0.95*
7	M	37	EHEC	Clinically improved	Normal	HD
8	M	55	Malignancy (gastric cancer), mitomycin/5-FU	Improved	NA	3.96†
9	F	31	Unknown	Improved	Normal	HD
10	F	61	Unknown	Improved	Normal	2.99‡
11	F	40	BMT (ALL), TMA: 10 wk after aPBSCT	Unchanged	Normal	HD
12	F	46	BMT (CML), TMA: 9 mo after aPBSCT	Unchanged	Normal	HD
13	M	62	BMT (MDS, secondary AML), TMA: 18 d after aPBSCT	Died	Normal	HD
14	F	44	Malignancy (anal cancer), mitomycine/5-FU & decreased vWFcP activity	Died	3% with CI	HD
15	F	66	Malignancy (mediastinal mass of unknown cause), no chemotherapy administered	Died	Normal	HD

5/15 are HSCT patients

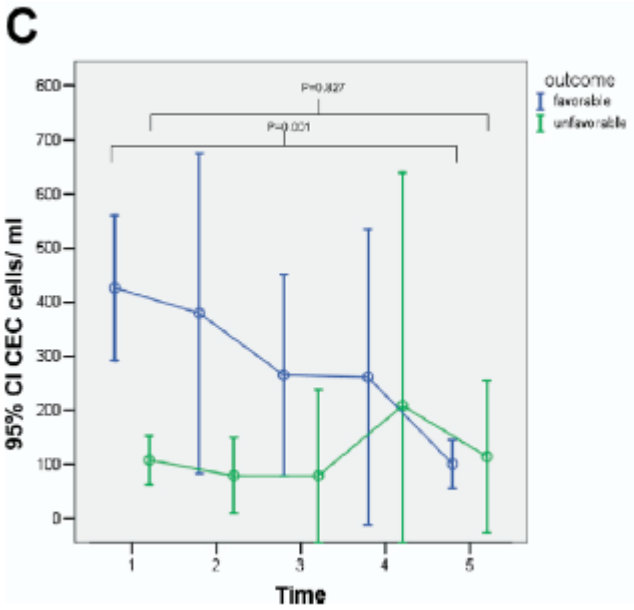


Elevated numbers of CECs are present in all TMA pts;

Elevated CECs correlate with a favorable outcome;

Plasma exchange decreases CECs level in pts with favorable outcome;

2/5 HSCT pts have a favorable outcome.



Hemopoietic stem cell trasplantation TA-TMA

Mechanisms of ENDOTHELIAL DAMAGE

aHUS

- Genetic mutations in Complement gene regulation (CFH, CFI, MCP, C3, CFHR5);
- Acquired defects → Neutralizing autoantibodies to Factor H.

TA-TMA

- High prevalence of a heterozygous CFHR3-CFHR1deletion; (JodeleS. Blood Rev 2015);
- Frequent presence of Factor H autoantibodies (JodeleS. Blood Rev 2015).
- Allo Abs and Complement role needs further studies.

Chronic Kidney Disease, Thrombotic Microangiopathy, and Hypertension Following T Cell-Depleted Hematopoietic Stem Cell Transplantation

Ilya G. Glezerman,[1] Kenar D. Jhaveri,[2] Thomas H. Watson,[3] Alison M. Edwards,[4] Esperanza B. Papadopoulos,[5] James W. Young,[5] Carlos D. Flombaum,[1] Ann A. Jakubowski[5]

Chronic kidney disease (CKD) is now an accepted long-term complication of allogeneic hematopoietic stem cell transplantation. Calcineurin inhibitors (CNI), which are used for prophylaxis and treatment of graft-versus-host disease (GVHD), have been associated with the development of nephrotoxicity. Hypertension (HTN) and thrombotic microangiopathy (TMA) are 2 comorbidities linked to CKD. T cell depletion (TCD) of stem cell grafts can obviate the need for the use of CNI. We conducted a retrospective analysis of 100 patients who underwent TCD transplantation: 30 in group A were conditioned without total-body radiation (TBI) and 70 in group B received a TBI containing regimen. None of the patients received CNI. The median age was 55.5 and 45 years for groups A and B, respectively. Eleven patients developed TMA, all in group B. The 2-year cumulative incidence of sustained CKD was 29.2% and 48.8% in group A and group B, respectively, with a mean follow-up of at least 21 months. CKD free survival was better in the non-TBI group ($P = .046$). Multivariable survival analysis revealed that exposure to TBI, older age, and TMA were risk factors for CKD. The incidence of new onset or worsening HTN was 6.7% and 25.7% ($P = .03$) in group A and B, respectively. The use of TBI ($P = .0182$) and diagnosis of TMA ($P = .0006$) predisposed patients to the development of HTN using univariable logistic regression models. Thus, despite the absence of CNI, a proportion of these older patients in both groups developed CKD and HTN.

Biol Blood Marrow Transplant 16: 976-984 (2010)

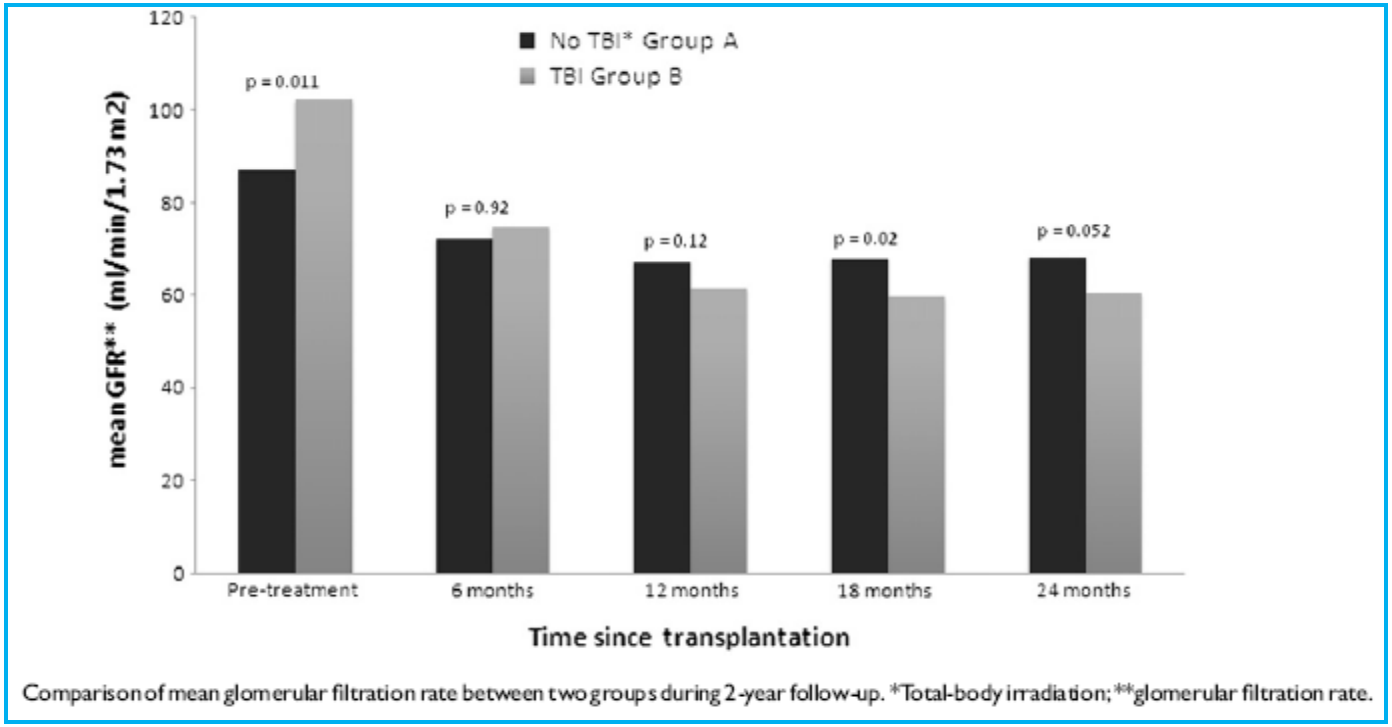
Table 1. Patient Characteristics.

	Group A N = 30	Group B N = 70	p-value
Median age	55.5	45.0	<0.0001
Gender			NS†
Male	15 (50.0%)	41 (58.6%)	
Female	15 (50.0%)	29 (41.4%)	
Diagnosis			0.004
Acute myelogenous leukemia	20 (66.7%)	33 (47.1%)	
Acute lymphocytic leukemia	1 (3.3%)	19 (27.1%)	
Chronic myelogenous leukemia	0 (0.0%)	7 (10.0%)	
Non-Hodgkin's lymphoma	4 (13.3%)	7 (10.0%)	
Myelodysplastic syndrome	5 (16.7%)	4 (5.7%)	
Donor-Recipient Match			NS
Matched	24 (80.0%)	60 (85.7%)	
Mismatched	6 (20.0%)	10 (14.3%)	
Donor-Recipient Relationship			0.01
Related	11 (36.7%)	45 (64.3%)	
Unrelated	19 (63.3%)	25 (35.7%)	
Pre-treatment GFR*(mean)	87.8 (SD‡=25.9)	102.3 (SD=23.9)	0.012
Other Baseline Co-morbidities			
Hypertension	5 (16.7%)	7 (10.0%)	NS
Diabetes	0 (0.0%)	2 (2.9%)	NS
Childhood hemolytic uremic syndrome	0 (0.0%)	1 (1.4%)	NS
Months Follow-up (mean)	21 (SD=4.9)	22 (SD=4.7)	NS
AKI** (first month post transplant)	4 (13.3%)	21 (30.0%)	NS
Alive at last follow up	26 (86.7%)	56 (80.0%)	NS
Acute GVHD***			
Grade 1	2 (6.7%)	4 (5.7%)	0.76943
Grade 2	3 (10.0%)	4 (5.7%)	
Grade 3	0 (0.0%)	2 (%2.9)	
No Acute GVHD	25 (83.3%)	60 (85.7%)	
Chronic GVHD			
Extensive	1 (%)	3 (%)	0.23953
Limited	0 (%)	6 (%)	
No Chronic GVHD	29 (%)	61 (%)	

Group A
no TBI

Group B
TBI

11 pts with TA-TMA, all in B group



Comparison of mean glomerular filtration rate between two groups during 2-year follow-up. *Total-body irradiation; **glomerular filtration rate.

2 years Cumulative Incidence sustained CKD:

- 29.2% in A group;
- 48.8% in B group.

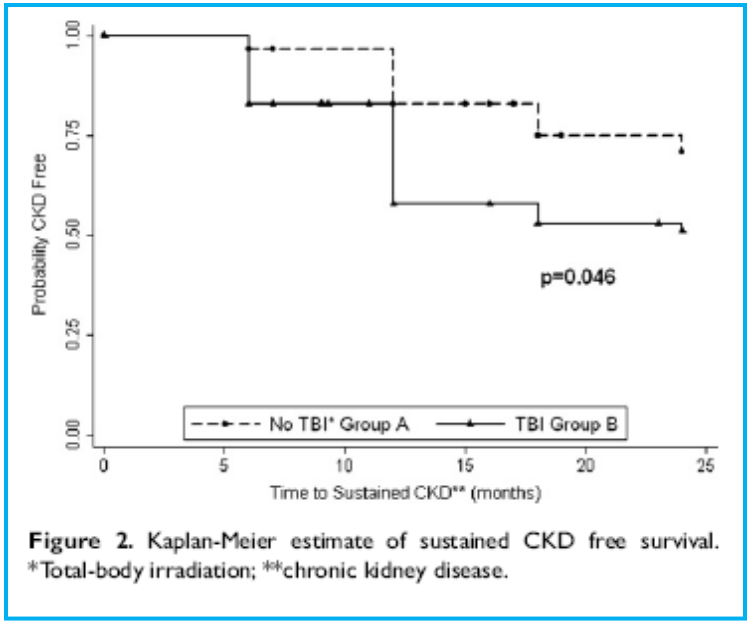


Figure 2. Kaplan-Meier estimate of sustained CKD free survival. *Total-body irradiation; **chronic kidney disease.

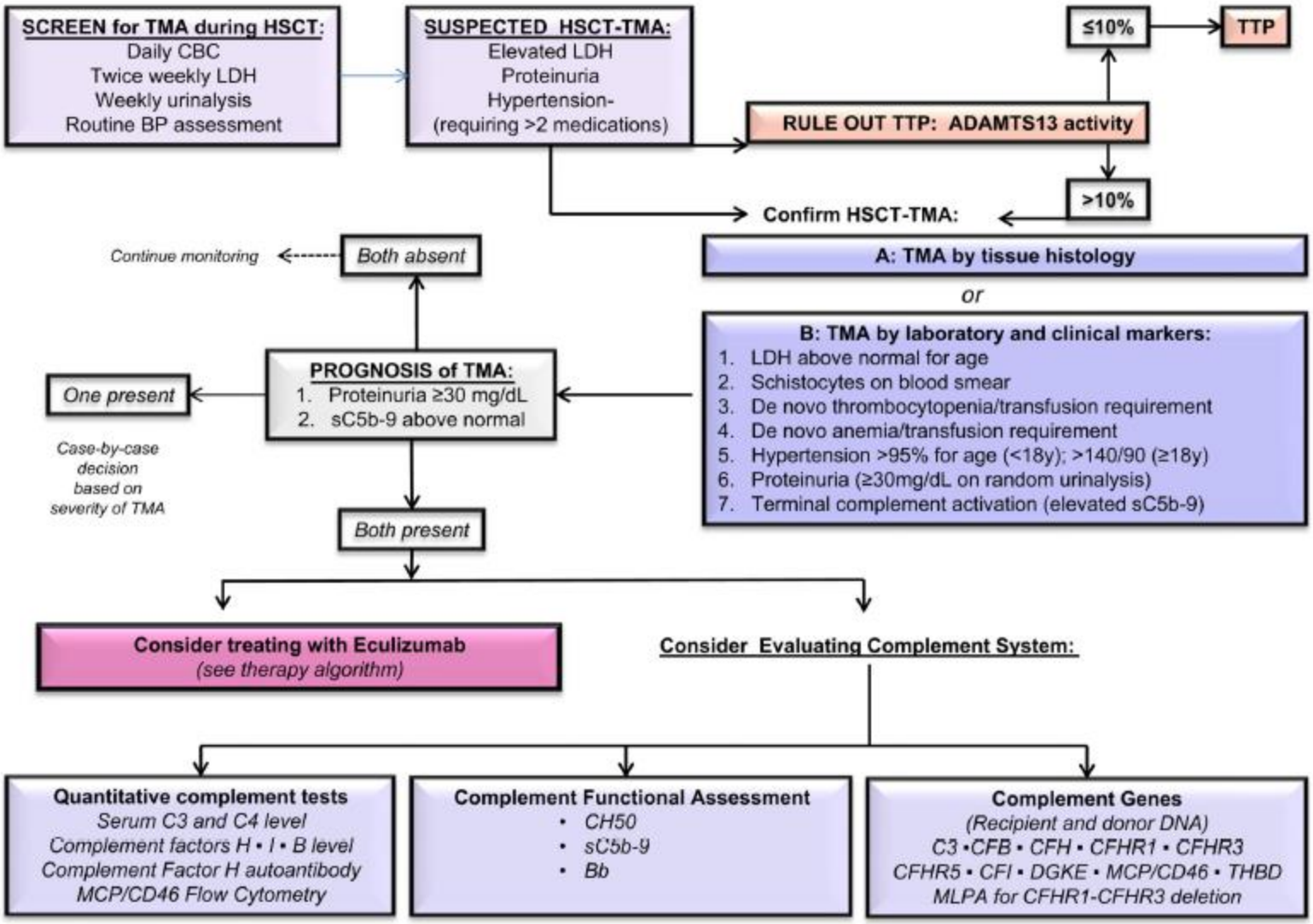
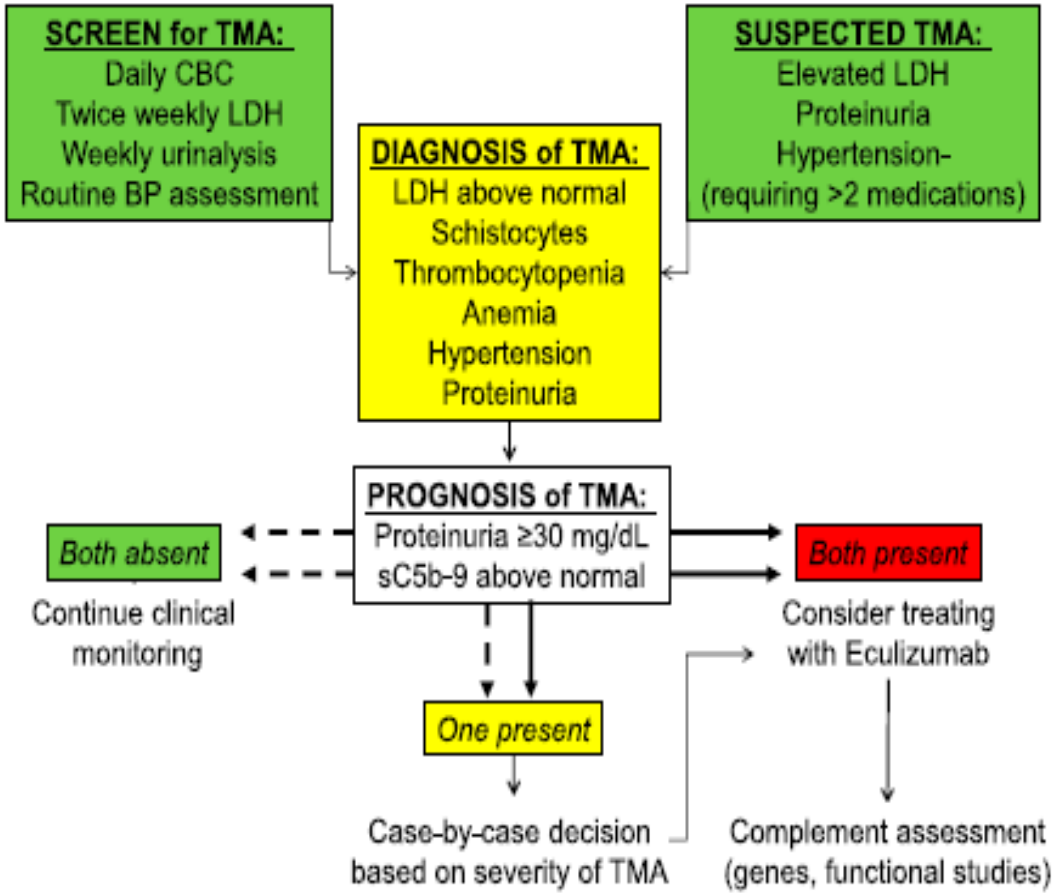


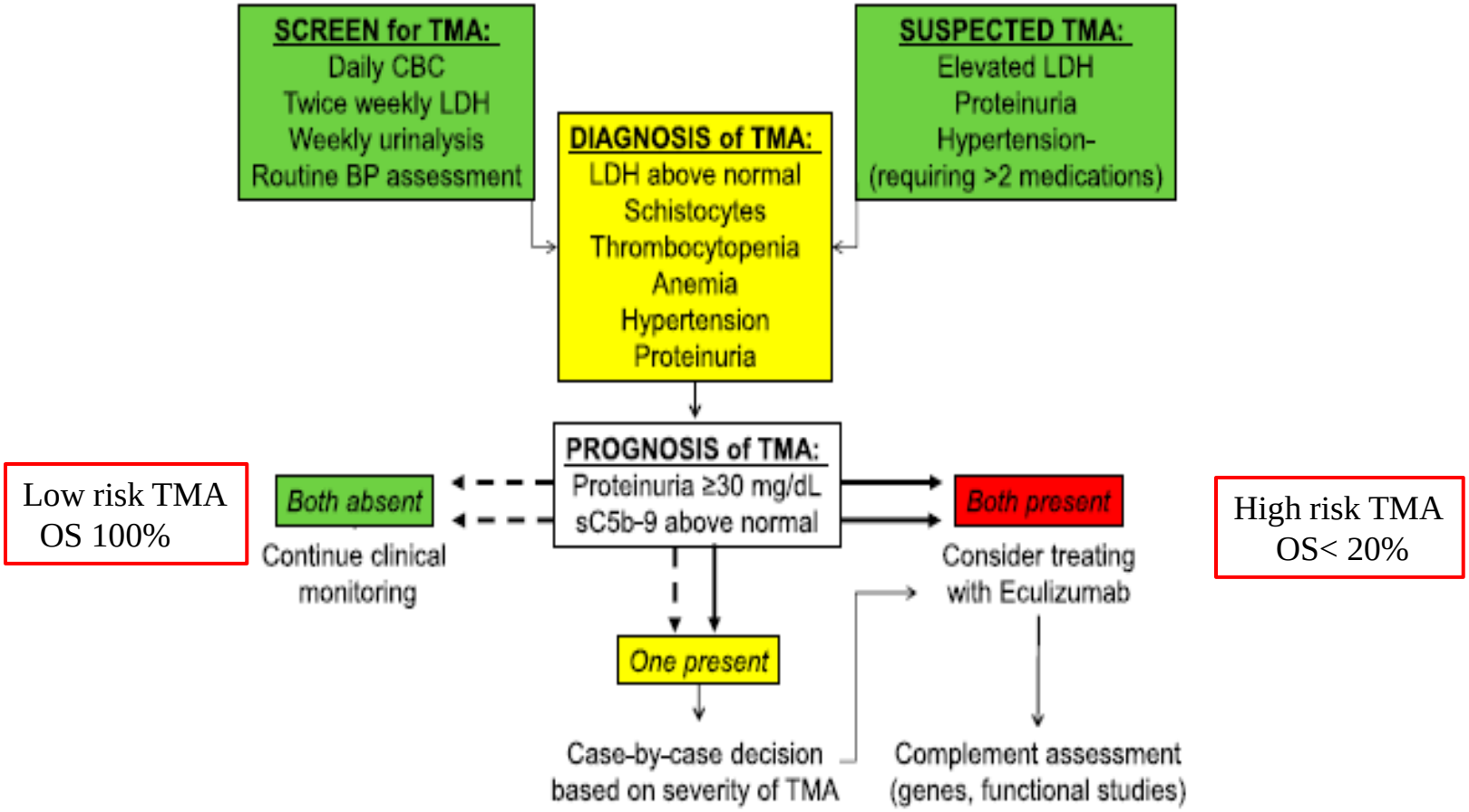
Fig. 3.
Diagnosis and risk assessment algorithm for TA-TMA after HSCT.

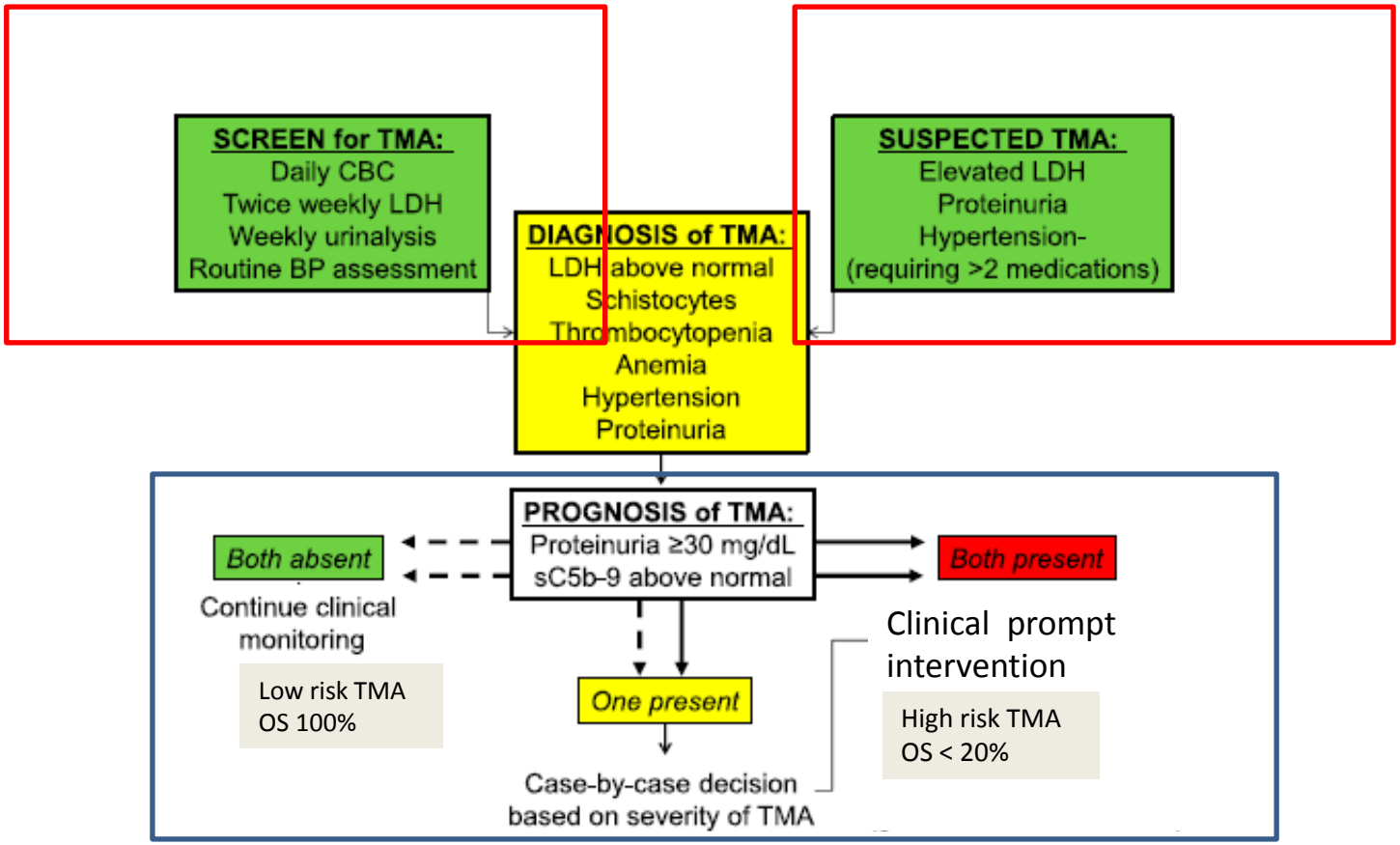
Sonata J.
Blood Rev. 2015 May

Algorithm for the evaluation of TMA after HSCT.



Algorithm for the evaluation of TMA after HSCT.





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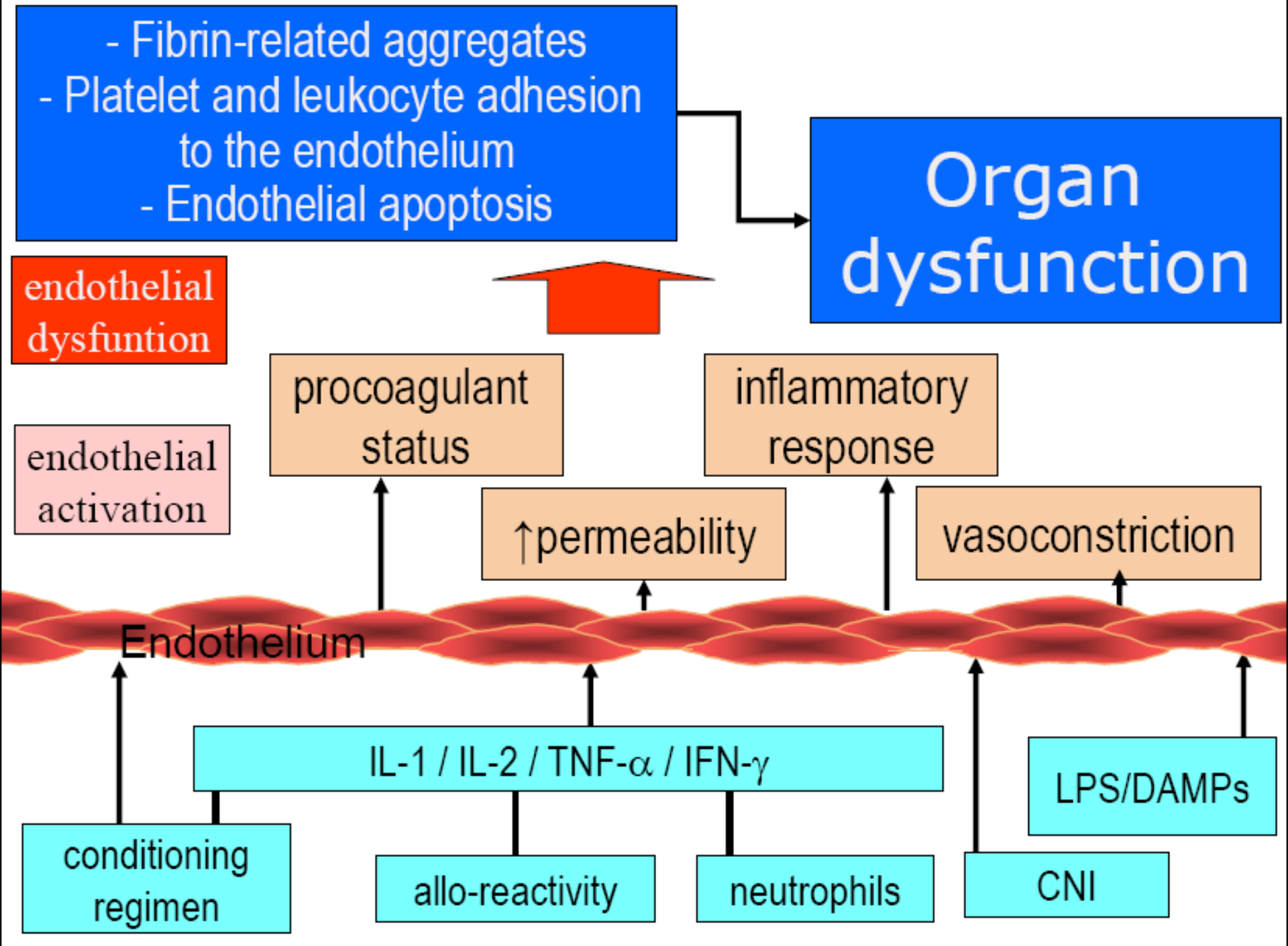
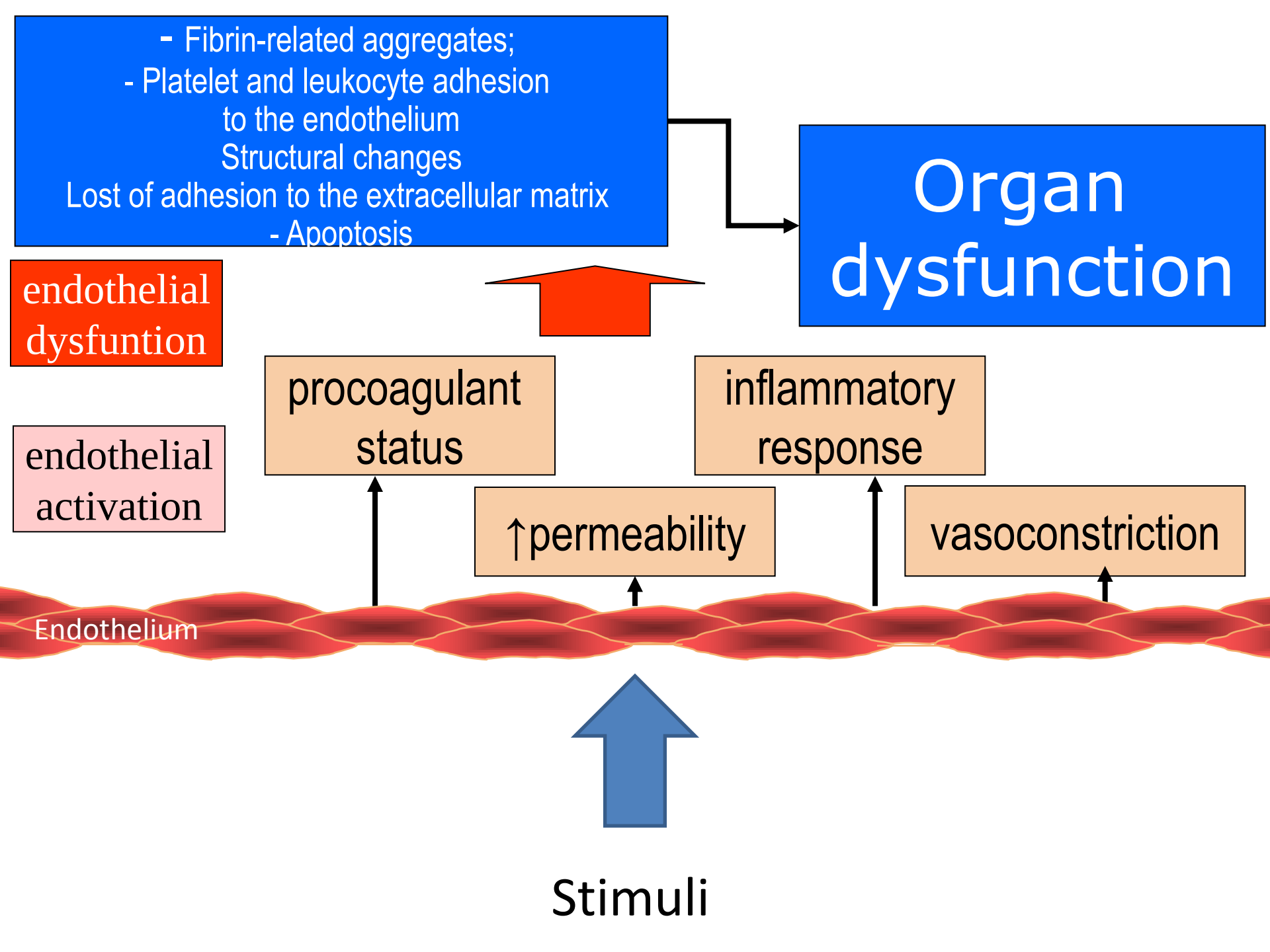
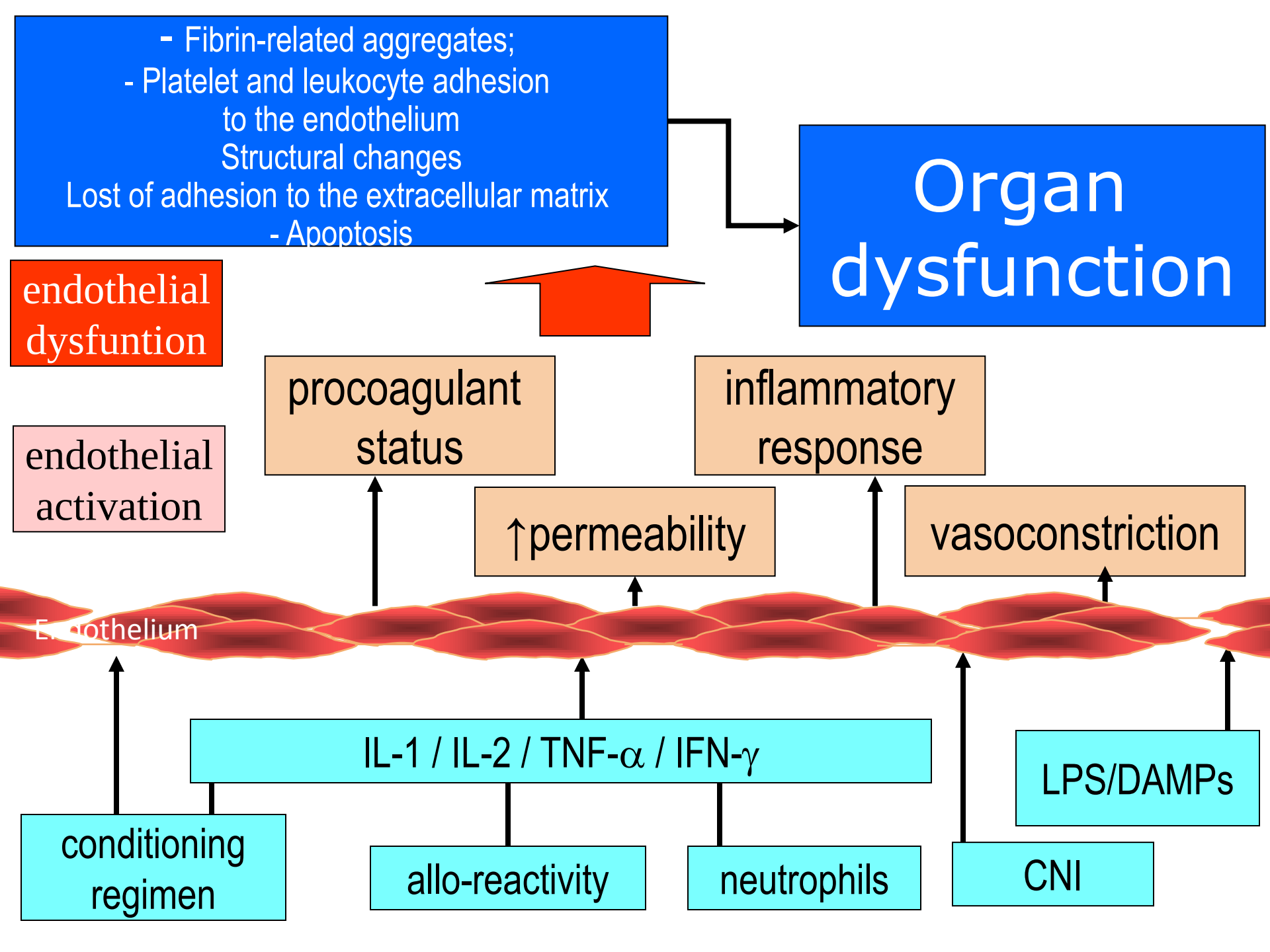
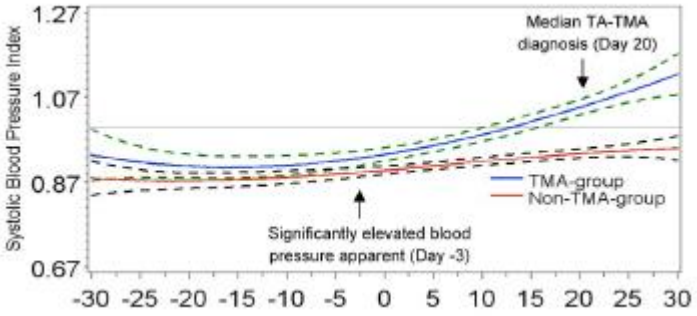

- Fibrin-related aggregates
- Platelet and leukocyte adhesion to the endothelium
- Endothelial apoptosis
Organ dysfunction
endothelial dysfuntion
procoagulant status
inflammatory response
endothelial activation
↑permeability
vasoconstriction
Endothelium
IL-1 / IL-2 / TNF-α / IFN-γ
LPS/DAMPs
conditioning regimen
allo-reactivity
neutrophils
CNI


- Fibrin-related aggregates;
- Platelet and leukocyte adhesion to the endothelium
Structural changes
Lost of adhesion to the extracellular matrix
- Apoptosis
Organ dysfunction
endothelial dysfuntion
procoagulant status
inflammatory response
endothelial activation
↑permeability
vasoconstriction
Endothelium
Stimuli


- Fibrin-related aggregates;
- Platelet and leukocyte adhesion to the endothelium
Structural changes
Lost of adhesion to the extracellular matrix
- Apoptosis
Organ dysfunction
endothelial dysfuntion
procoagulant status
inflammatory response
endothelial activation
↑permeability
vasoconstriction
Endothelium
IL-1 / IL-2 / TNF-α / IFN-γ
LPS/DAMPs
conditioning regimen
allo-reactivity
neutrophils
CNI



Proteinuria

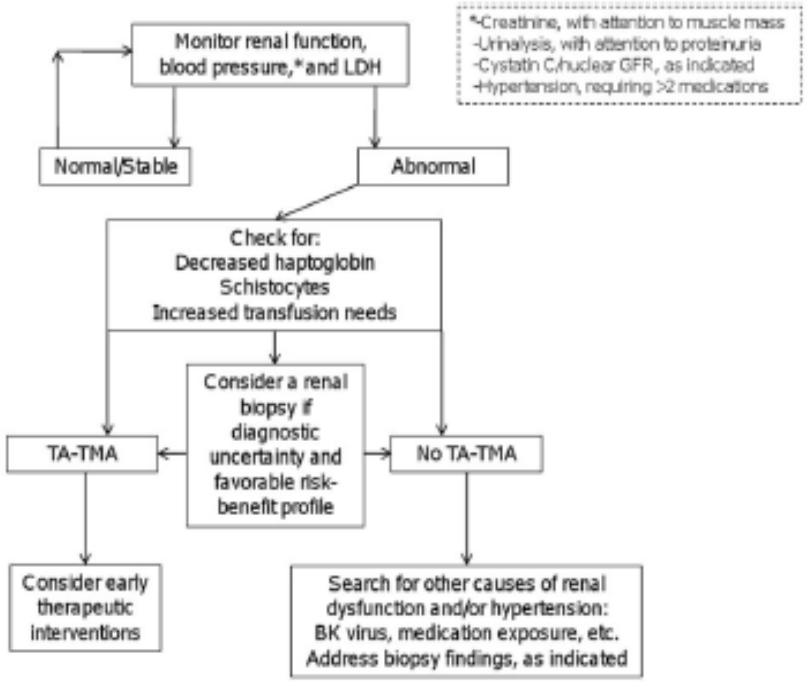


Figure 4. A "renal-centric" approach to detect TA-TMA. Because TA-TMA is unlikely to occur without alterations in renal function or blood pressure, careful routine monitoring of these parameters in the context of HSCT can aid in the differential diagnosis. This includes close attention to creatinine (and its dependence on muscle mass), other potentially more reliable measures of GFR (ie, cystatin C), urinalysis findings, and blood pressure readings. Evidence for proteinuria should be quantified by a first-morning spot urine protein-to-creatinine ratio (> 0.2 mg/mg is elevated). Patients with elevated LDH, abnormal renal findings or elevated blood pressure or a combination should be carefully screened for TA-TMA according to current guidelines and clinical findings. In the presence of diagnostic uncertainty, the benefit of tissue diagnosis, especially renal biopsy, should be carefully weighed against procedural risks. Potential therapeutic interventions to consider for patients with TA-TMA include calcineurin inhibitor withdrawal, plasma exchange, and rituximab. Patients without TA-TMA should be assessed for other causes of renal dysfunction or hypertension, including, but not limited to, BK virus and medication exposure (eg, steroids, calcineurin inhibitors, chemotherapeutic agents, or antimicrobials).

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Response of TMA to tacrolimus/sirolimus interventions

Intervention	Initial Interventions	Final Intervention
D/C Sirolimus responded/treated	9/9	11/11
D/C Tacrolimus * responded/treated	5/8	3/3
D/C Tacro & Siro ** responded/treated	2/6	5/12
Dose Modified * responded/treated	6/7	3/4

The number of patients who responded to a treatment is given over the number who were treated. The initial intervention shows first treatment responses in each category and final shows the results of the last treatment attempted. D/C – discontinued

* One patient was treated with dose reduction of sirolimus, discontinuation of tacrolimus and plasma exchange, and responded to the overall therapy.

** Seven patients were treated with discontinuation of both tacrolimus and sirolimus as well as plasma exchange, and three patients responded to the overall therapy.

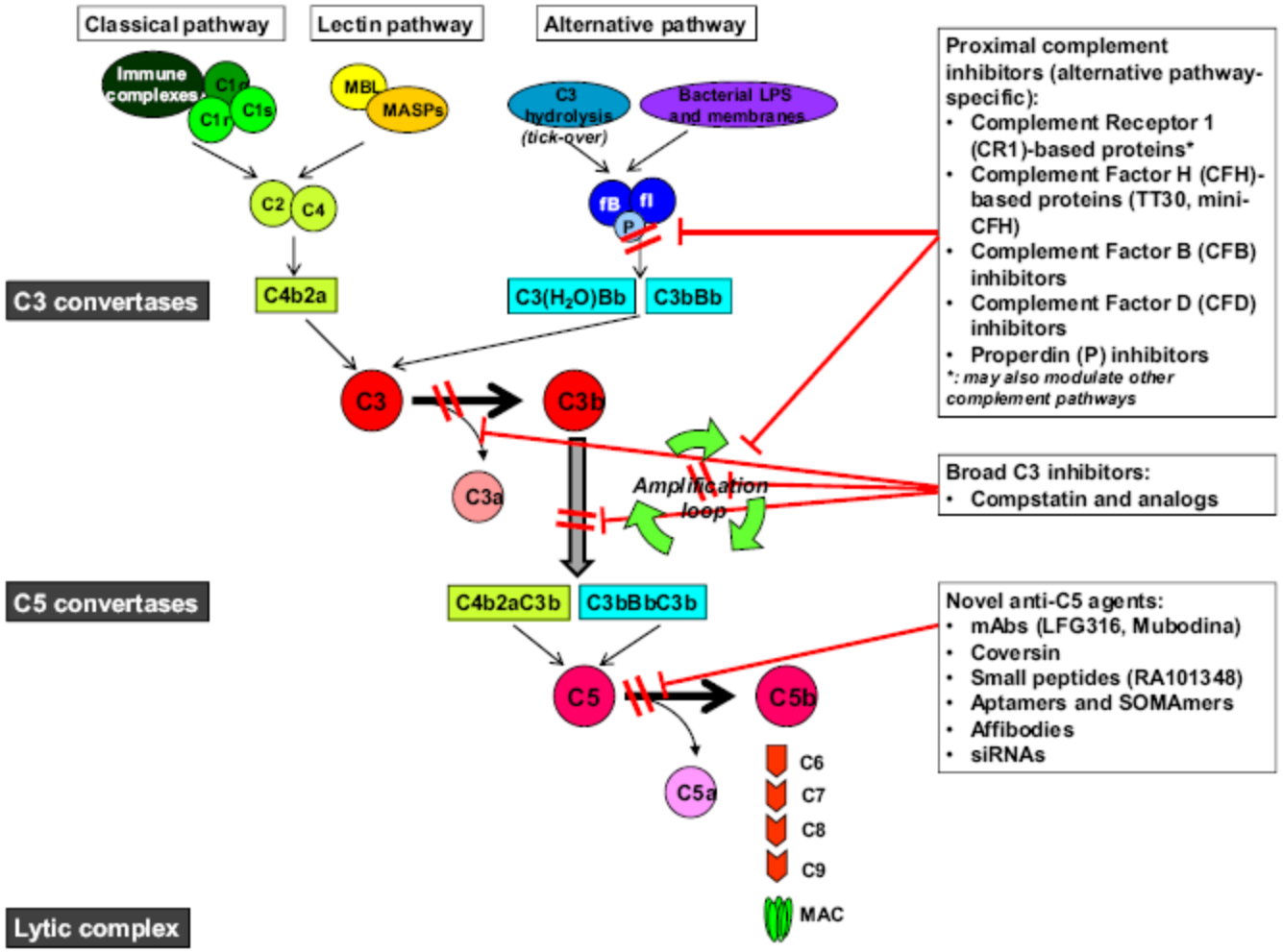
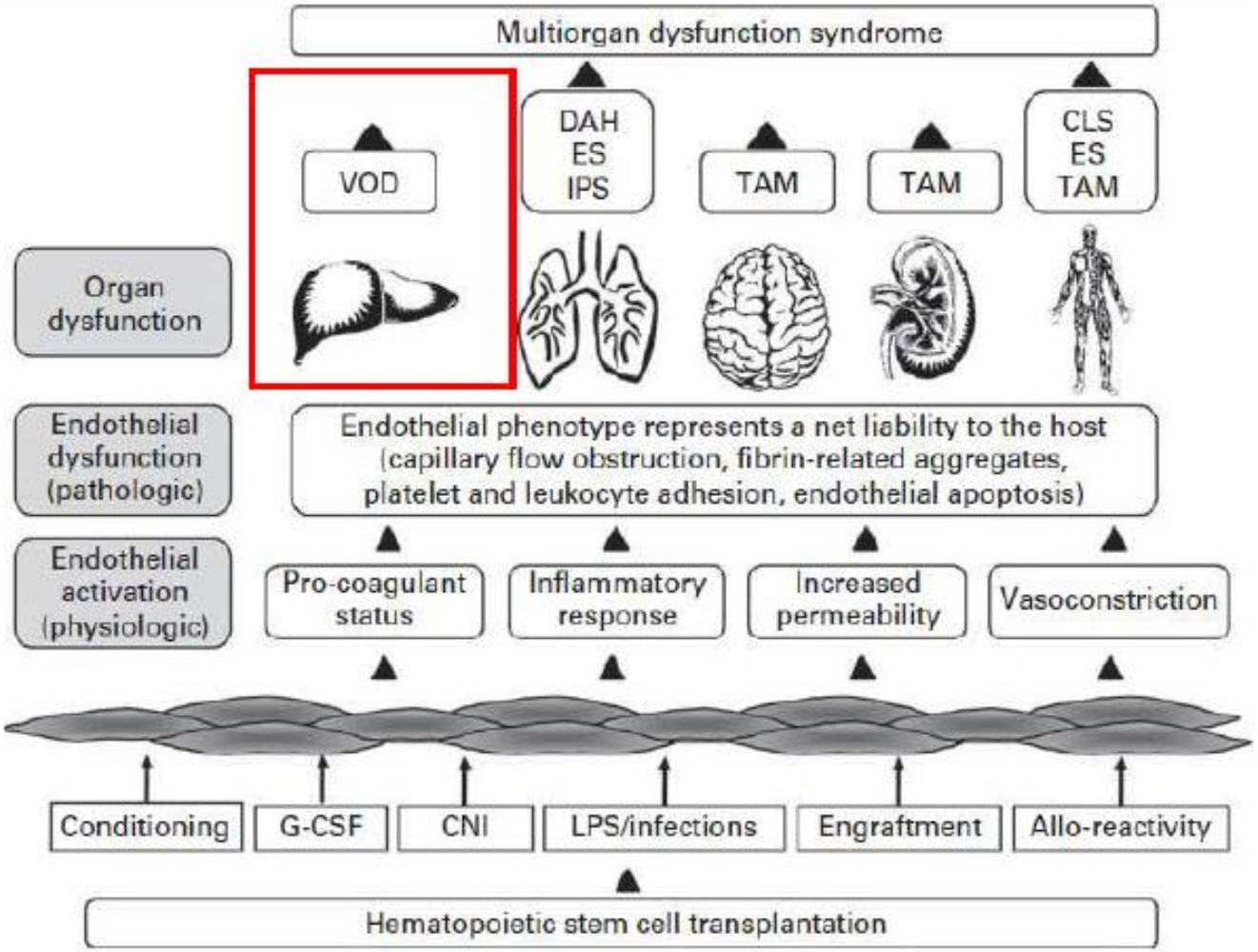


Fig. 1. Complement system and its targeted modulation.
Overview of the complement cascade, including all main functional components and physiologic regulators. The three activating pathways (alternative, classical, and mannose/lectin) are individually depicted, together with the alternative pathway amplification loop. Candidate inhibitors are grouped according to their specific target; their modulatory effects are indicated by red lines intercepting specific steps of the complement cascade. See also main text for a more detailed description.

Endothelial complications after HSCT

The clinical spectrum



Bone Marrow Transplantation (2011) 46, 1495–1502

Eculizumab (Soliris- Alexion): posologia in aHUS (da scheda tecnica):

Per il trattamento della sindrome emolitico uremica atipica (SEUa):
Il regime posologico per la terapia della SEUa in pazienti adulti (≥18 anni) consiste in una fase iniziale di 4 settimane seguita da una fase di mantenimento:

- Fase iniziale: 900 mg di Soliris somministrati con un'infusione endovenosa di 25 – 45 minuti ogni settimana per le prime 4 settimane.
- Fase di mantenimento: 1200 mg di Soliris somministrati con un'infusione endovenosa di 25 – 45 minuti nella quinta settimana, seguita da 1200 mg di Soliris somministrati con un'infusione endovenosa di 25 – 45 minuti ogni 14 giorni ± 2 giorni (vedere paragrafo 5.1).

Pazienti pediatrici:
Nei pazienti pediatrici con peso corporeo ≥ 40 kg affetti da EPN e SEUa è utilizzato rispettivamente lo stesso regime posologico raccomandato per gli adulti.

In pazienti pediatrici affetti da EPN e SEUa di peso inferiore a 40 kg, il regime posologico di Soliris è:

Peso corporeo del paziente	**Fase iniziale**	**Fase di mantenimento**
da 30 a <40 kg	600 mg alla settimana x 2	900 mg alla settimana 3; poi 900 mg ogni 2 settimane
da 20 a <30 kg	600 mg alla settimana x 2	600 mg alla settimana 3; poi 600 mg ogni 2 settimane
da 10 a <20 kg	600 mg alla settimana x 1	300 mg alla settimana 2; poi 300 mg ogni 2 settimane
da 5 a <10 kg	300 mg alla settimana x 1	300 mg alla settimana 2; poi 300 mg ogni 3 settimane

Hemopoietic stem cell trasplantation TA-TMA

Prognosis

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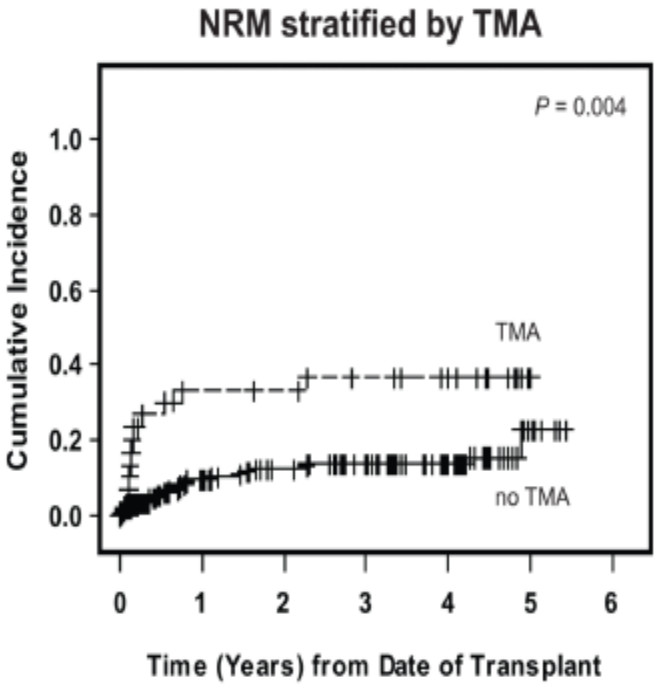
Hazard Risks for NRM and TMA NRM

A. NRM Risk

Parameter	Value	N	# of events	Hazard Risk Ratio (95% CI)	p value
Sirolimus	< 9.9	132	21	Baseline	
14-day levels	≥9.9	44	12	1.67 (0.79-3.51)	0.18
TMA	No TMA	146	22	Baseline	
	Definitive TMA	30	11	2.76 (1.29-5.92)	0.009

B. TMA Risk

Parameter	Value	N	# of events	Hazard Risk Ratio (95% CI)	p value
Conditioning	Reduced intensity	106	9	Baseline	
	Fully myeloablative	70	21	3.47 (1.60-7.53)	0.002
Acute GVHD	Grade 0-1	95	8	Baseline	
	Grade 2-4	81	22	3.04 (1.38-6.71)	0.006
Sirolimus	< 9.9	131	18	Baseline	
14-day levels	≥9.9	45	12	2.19 (1.13-4.27)	0.02



Common pathogenesis of the vascular endothelial syndromes developed early after HSCT