GITMO

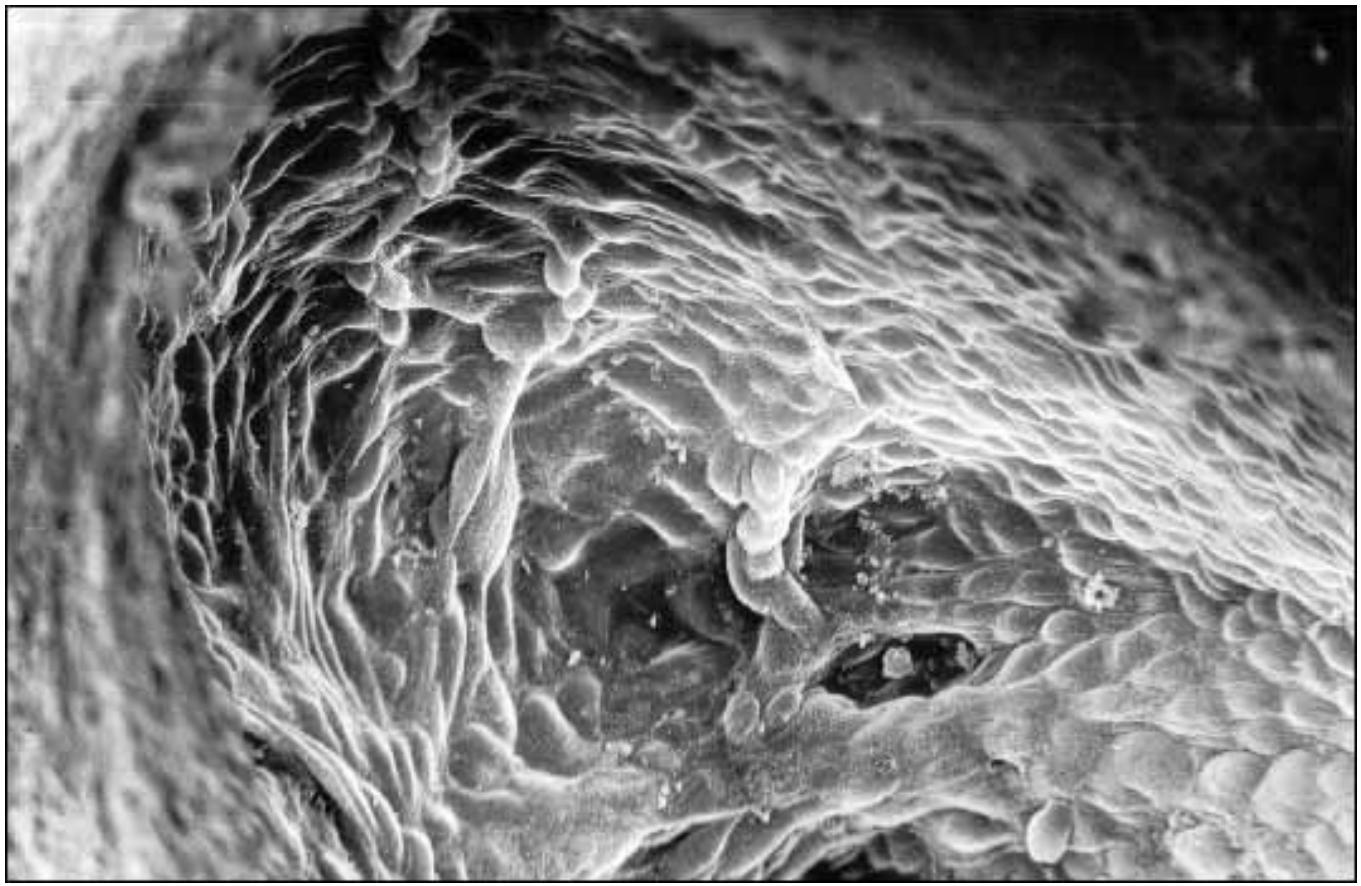
Emopatie non maligne e trapianto:

RARE POST-TRANSPLANT COMPLICATIONS

Management of endothelial complications

Francesco Onida
Centro Trapianti Midollo Osseo
Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico
Università degli Studi di Milano

The endothelium

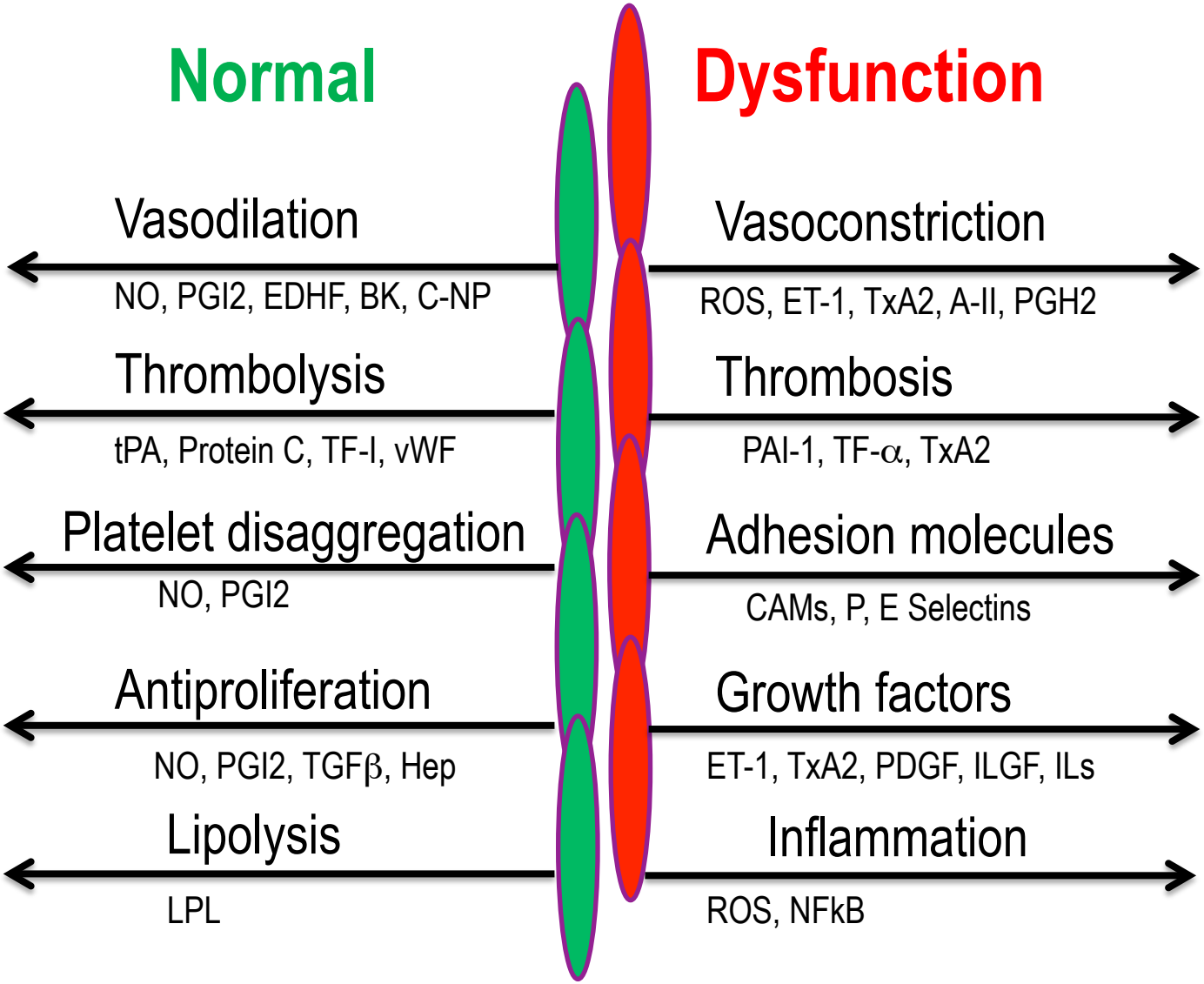


The human body contains 10^{13} endothelial cells weighing 1.5 kg and covering a surface of up to 1000 m^2

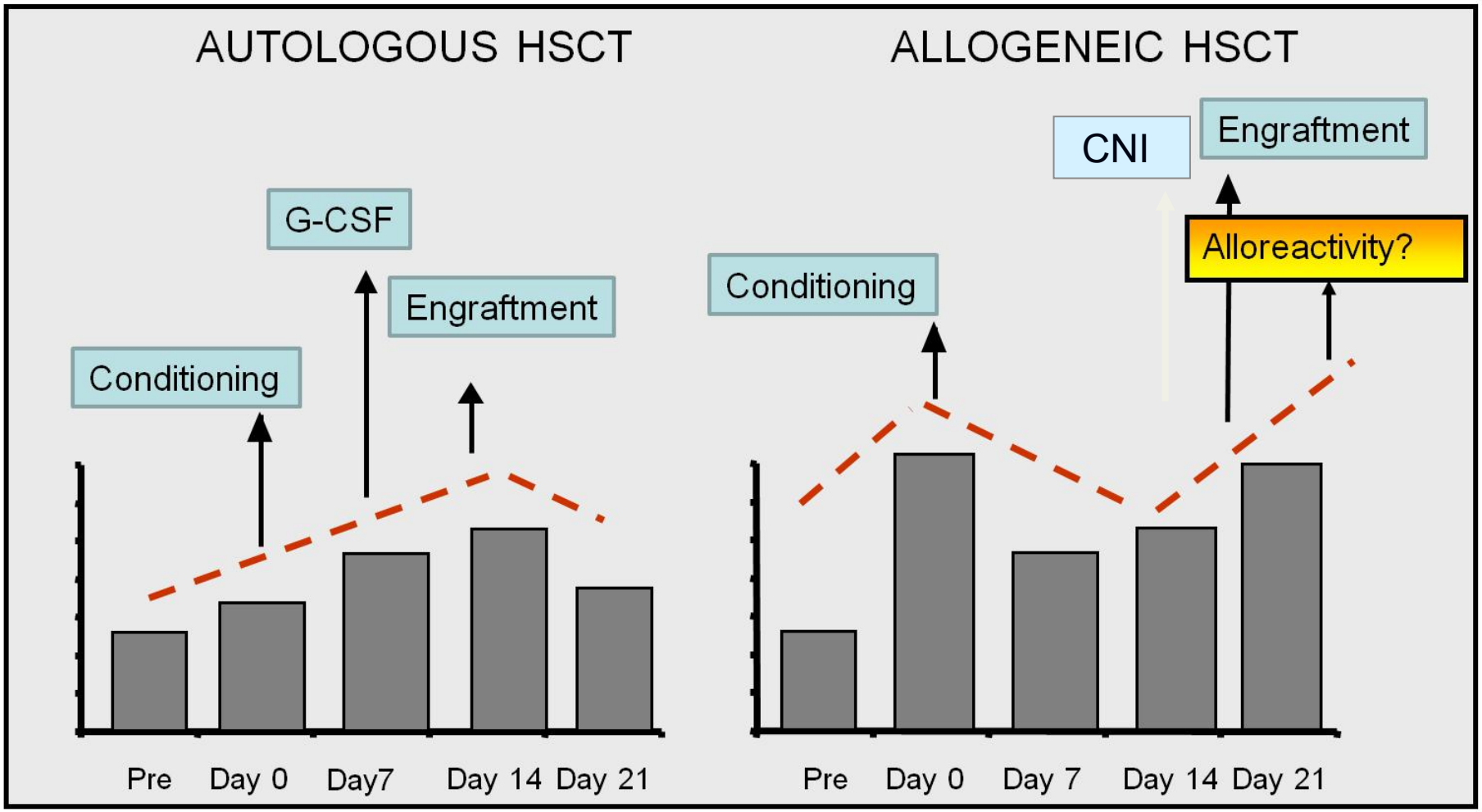
Vascular endothelium

- Acts as a barrier between flowing blood and vascular wall
- Regulates vascular growth, platelet function and coagulation
- Modulates vascular tone, caliber and blood flow
- Responds to numerous humoral, neural and mechanical stimuli
- Sinthesizes and releases vasoactive substances (eg, nitric oxid)

Regolatory functions of the endothelium



Endothelial damage after HSCT

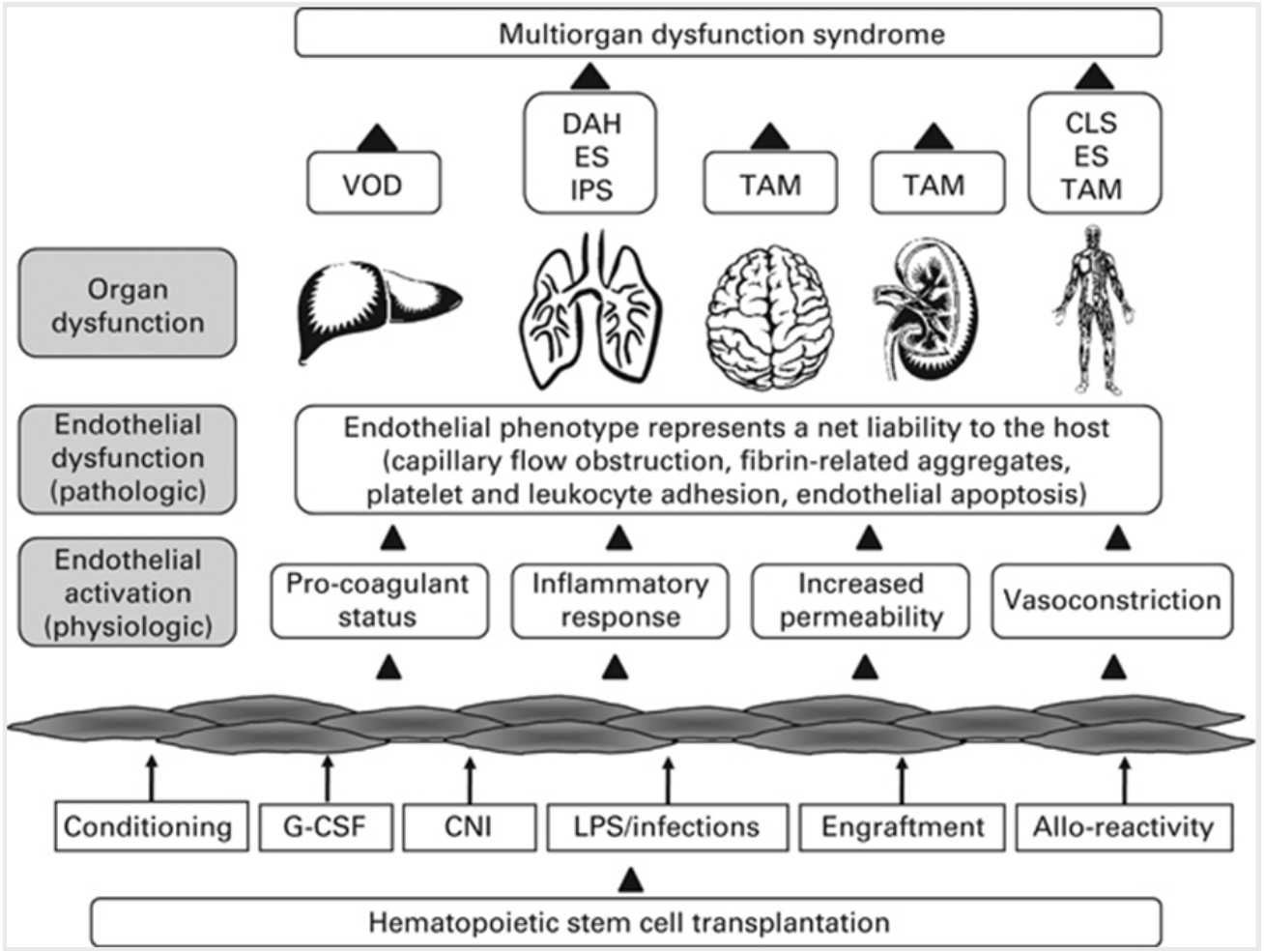


Courtesy of E.Carreras

Vascular endothelial syndromes after HSCT

- **Hepatic Veno-Occlusive Disease (VOD)**
- **Transplant-Associated Thrombotic MicroAngiopathy (TA-TMA)**
- Capillary Leak Syndrome (CLS)
- Diffuse Alveolar Haemorrhage (DAH)
- Idiopathic Pneumonia Syndrome (IPS)
- **Engraftment Syndrome (ES)**
- Graft-versus-Host Disease (GvHD)

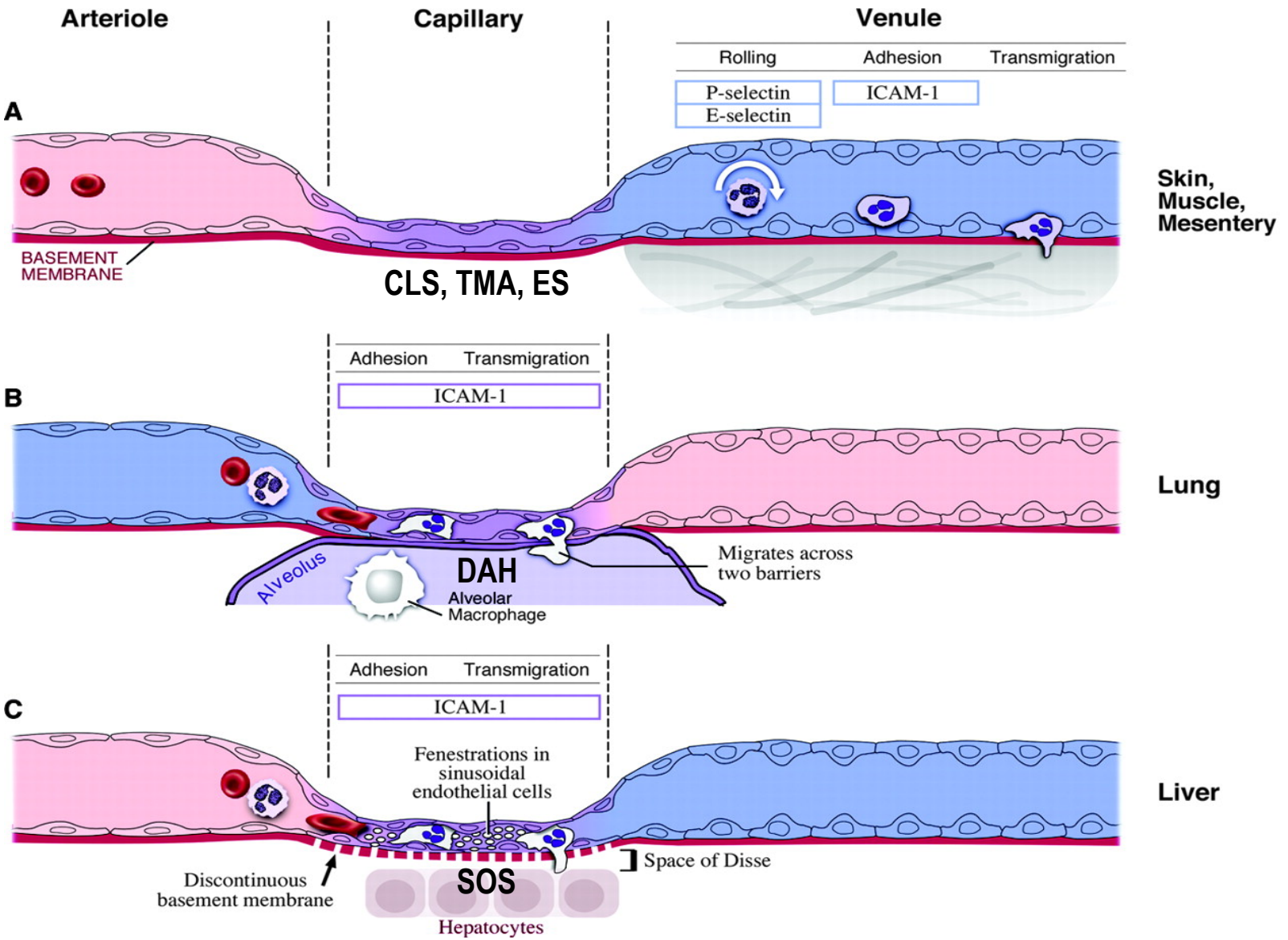
Vascular injuries to the endothelium post HSCT



CLS, capillary leak syndrome; CNI, calcineurin inhibitors; DAH, diffuse alveolar haemorrhage; ES, engraftment syndrome; G-CSF, granulocyte-colony stimulating factor; HSCT; haematopoietic stem cell transplantation; IPS, idiopathic pneumonia syndrome; LPS, lipopolysaccharide; TAM, transplant-associated microangiopathy; VOD, veno-occlusive disease

Carreras E & Diaz-Ricart M. *Bone Marrow Transplant* 2011;46:1495–1502

Endothelial syndromes: common aetiology



William C. Aird Circulation Research. 2007;100:158-173

Early complications of endothelial origin after HSCT

- Observed within the first 30-60 days after HSCT
- Overlapping clinical features and imprecise diagnostic criteria
- Share common pathogenic mechanisms
- Wide spectrum of presentation and variable outcomes → may be life threatening or lethal (irreversible MOF)

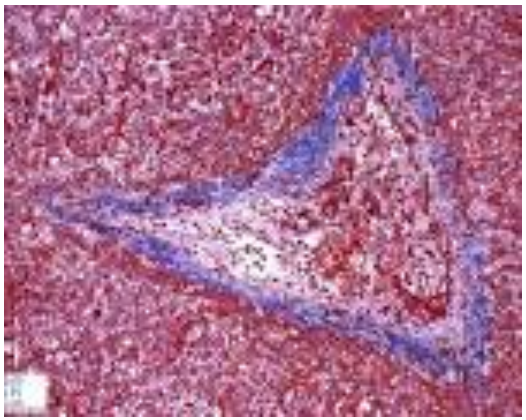
Hepatic veno-occlusive disease (VOD)

- Veno-occlusive disease (VOD), also known as *sinusoidal obstruction syndrome (SOS)*, is a potentially life-threatening complication of haematopoietic stem cell transplantation (HSCT)

- Mean incidence ranges between 8% and 14%

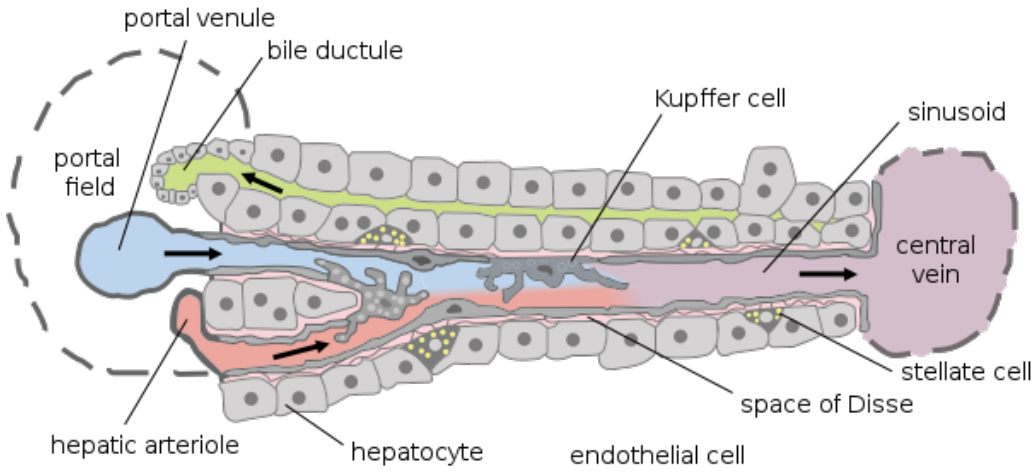
- The conditioning regimens given before HSCT result in the production of toxic metabolites by the hepatocytes in the liver

- This ultimately leads to VOD, characterised by:
  - Increased thrombosis and decreased fibrinolysis
  - Sinusoidal damage and narrowing
  - Inflammation



Richardson PG et al. Expert Opin Drug Saf 2013;12:123–136.

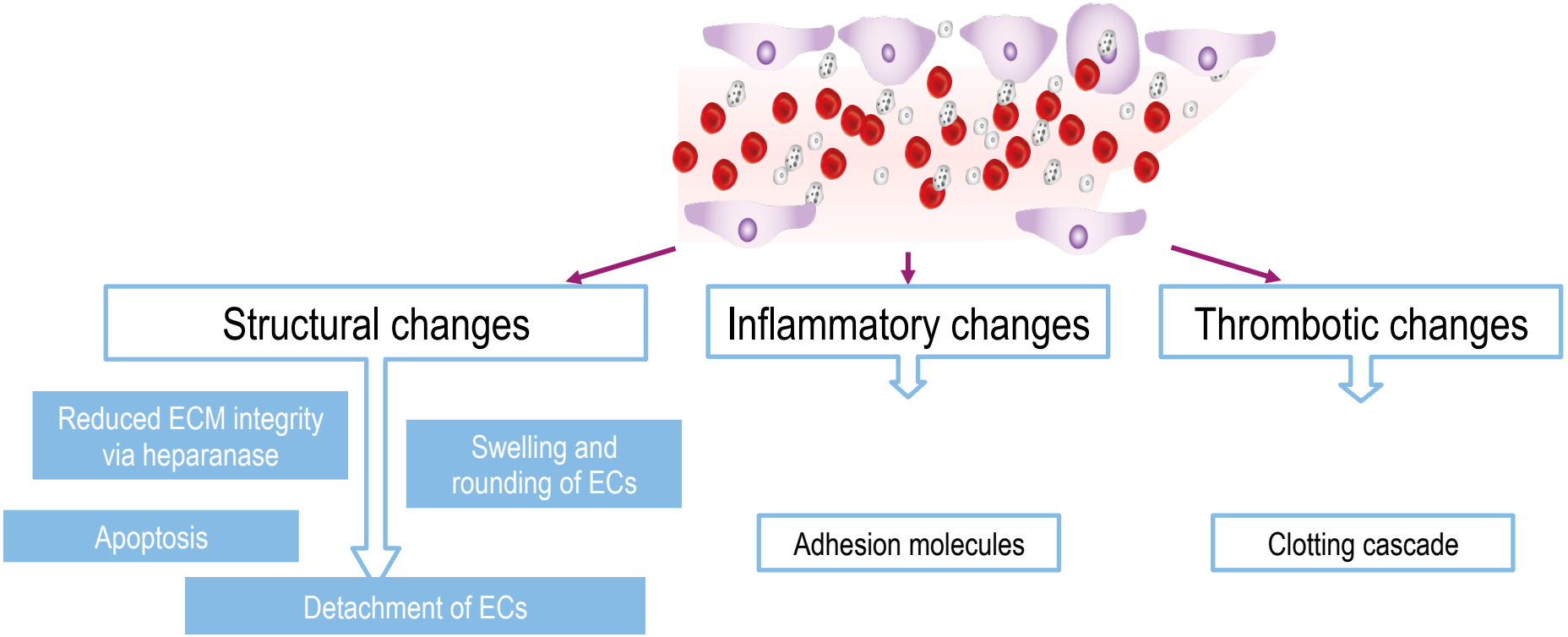
Structure and role of hepatic sinusoids



- The sinusoids are small capillary-like blood vessels within the liver that are lined by sinusoidal endothelial cells
- Sinusoidal endothelial cells play an important role in the function of the sinusoids as:
  - *selective sieves* for substances passing from the blood to hepatocytes
  - *a scavenger system* which clears the blood from many different macromolecular waste products

Wisse E et al. Toxicol Pathol 1996;24:100–111

VOD Pathophysiology



Structural changes result from[1,2]:
- **↑ heparanase activity contributing to reduced EC membrane integrity**
- **rounding up and swelling of ECs triggering apoptosis, inducing a detachment of ECs**

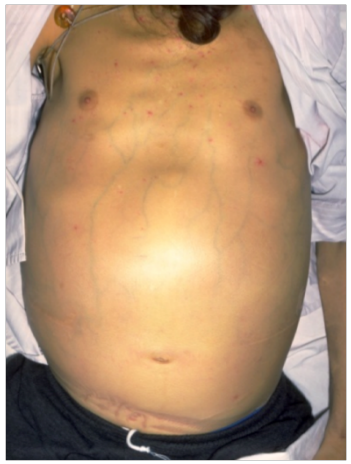
The EC dysfunction also leads to an inflammatory response resulting in expression of adhesion molecules, which attract leucocytes from the blood stream that adhere and move into the space of Disse[1]

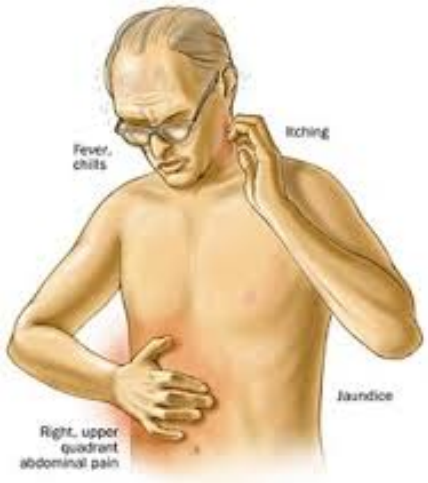
In addition, EC dysfunction leads to a shift of the physiologic anti-thrombotic state to a pro-thrombotic state which triggers the activation of a clotting cascade[3]

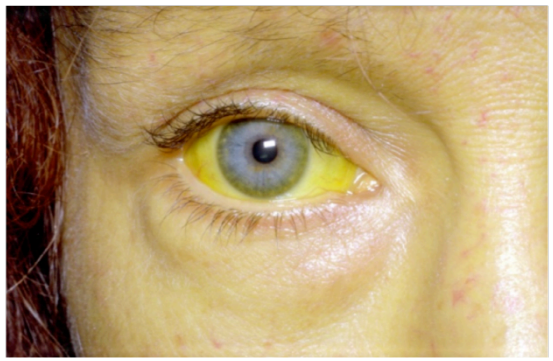
Richardson *et al*. *Ther Adv Hematol* . 2012; 3(4) 253–265; DeLeve LD. Chapter 2- Part 1. Vascular Liver Disease: Mechanisms and Management. New York: Springer 2011. Davis GE and Senger DR. Circ Res 2005; 97(11): 1093-1107Falanga *et al*., Leukemia. 2003;17, 1636–1642

Clinical presentation of VOD

- VOD is characterised by
  - Rapid weight gain
  - Ascites
  - Painful hepatomegaly
  - Jaundice
  - Right upper quadrant pain
- Symptoms usually present within the first 3–4 weeks following HSCT, but can occur later
- VOD is a progressive disease:
  - Severe VOD is associated with multi-organ failure and a high mortality rate (>80%)







Bearman SI. *Blood* 1995;85:3005–3020; McDonald GB et al. *Hepatology* 1984;4:116–122; Carreras E. Early complications after HSCT. In: Apperley J, Carreras E, Gluckman E Masszi T eds. ESH-EBMT Handbook on Haematopoietic Stem Cell Transplantation. Genova: Forum Service Editore, 2012 pp 176–95; Coppell JA et al. *Biol Blood Marrow Transplant* 2010;16:157–168

Severe VOD is fatal in >80% of cases

- Symptoms of weight gain, blood bilirubin levels, oedema and ascites all increase with the severity of VOD, however the incidence of death increases dramatically with severe VOD (sVOD)
- Death resulting from sVOD can be due to a number of factors:
  - Kidney or heart failure
  - Respiratory failure and pleural effusion (excess fluid building up around the lungs)
  - Encephalopathy (a disorder of the brain)
  - Bleeding in the lungs or intestines
  - Infection
  - Multi-organ failure

The mortality rate of severe VOD is in excess of 80%[1], in comparison to 23% and 9% for moderate and mild VOD[2], respectively

Coppell JA et al. Biol Blood Marrow Transplant 2010;16:157–168; McDonald GB et al. Ann Intern Med 1993;118:255–267; Baron F et al. Haematologica 1997;82:718–72; Kumar S et al. Mayo Clin Proc 2003;78:589–598.

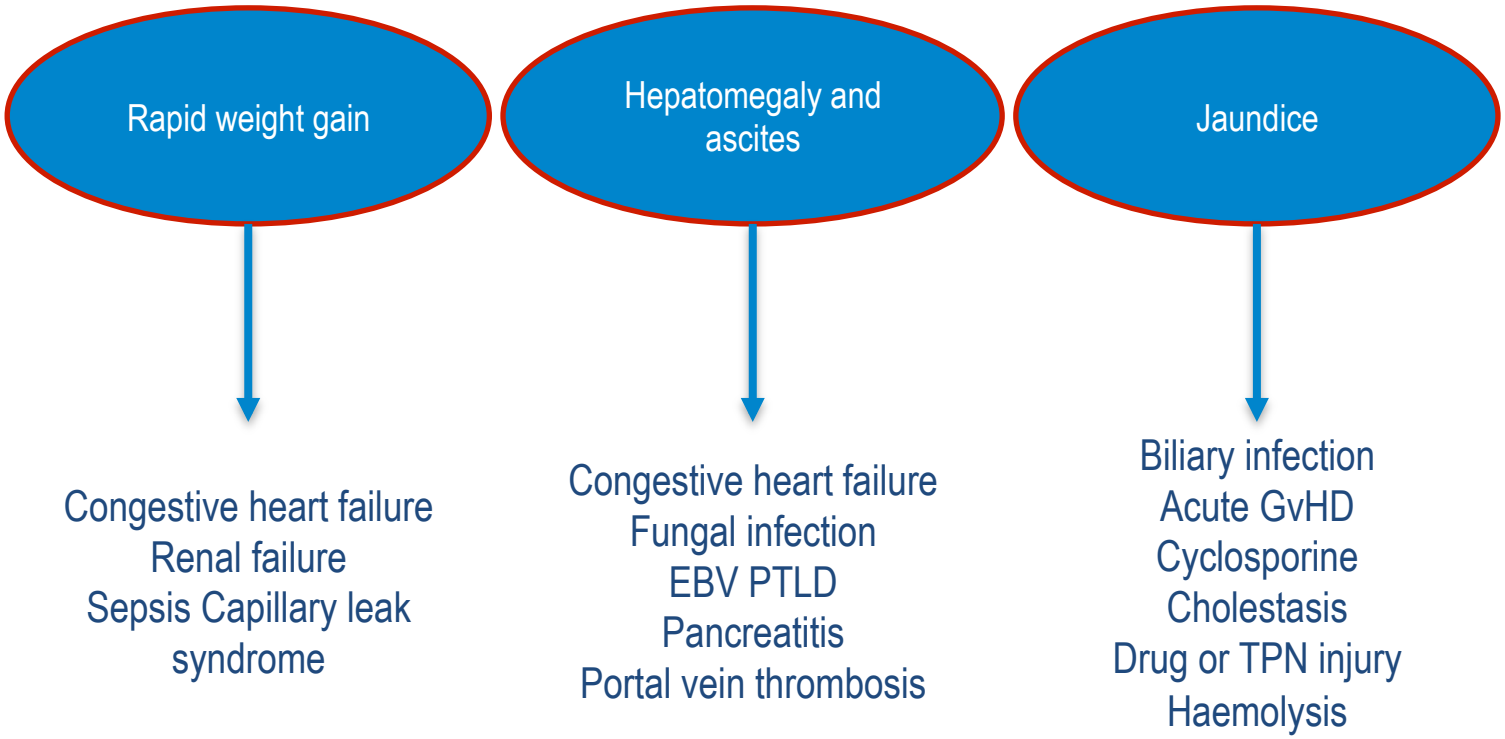
New EBMT criteria for SOS/VOD diagnosis in adults

Classical SOS/VOD	Late onset SOS/VOD
In the first 21 days after HSCT	>21 days after HSCT
Bilirubin ≥ 2 mg/dL AND two of the following criteria must be present: - Painful hepatomegaly - Weight gain >5% - Ascites	Classical VOD/SOS beyond day 21 OR Histologically proven SOS/VOD OR Two or more of the following criteria must be present: - Bilirubin ≥ 2 mg/dL (or 34 µmol/L) - Painful hepatomegaly - Weight gain > 5% - Ascites AND Hemodynamical or/and ultrasound evidence of SOS/VOD

Mohty M et al. BMT 2016;51:906-912

Differential diagnosis of VOD

VOD is a diagnosis of exclusion



EBV, Epstein–Barr virus; GvHD, graft-versus-host disease; TPN, total parental nutrition

Eisenberg S. *Oncol Nurs Forum* 2008;3:385–397

Risk factors for SOS/VOD in adults

Transplant-related factors

- Unrelated donor
- HLA-mismatched donor
- Non T-cell depleted transplant
- Myeloablative conditioning regimen
- Oral or high-dose busulfan-based regimen
- High-dose TBI-based regimen
- Second HSCT

Patient and disease related factors

- Older age
- Karnofsky score below 90%
- Metabolic syndrome
- Female receiving norethisterone
- Advanced disease (beyond second CR or relapse/refractory)
- Thalassemia
- Genetic factors (GSTM1 polymorphism, C282Y allele, *MTHFR* 677CC/1298CC haplotype)

Hepatic related

- Transaminases >2.5 ULN
- Serum bilirubin > 1.5 ULN
- Cirrhosis
- Active viral hepatitis
- Abdominal or hepatic irradiation
- Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin
- Hepatotoxic drugs
- Iron overload

Mohty M et al. BMT 2016;51:906-912

Risk factors for SOS/VOD in pediatric patients

- Hemophagocytic lymphohistiocytosis
- Osteopetrosis
- High dose auto-HSCT in neuroblastoma
- Young age (<2 yrs)
- Low weight
- JMML
- Second myeloablative HSCT

Mohty M et al. BMT 2016;51:906-912

New EBMT criteria for severity grading of a suspected SOS/VOD in adults

	Mild*	Moderate*	Severe	Very severe-MOD/MOF**
Time since first clinical symptoms of SOS/VOD***	> 7 days	5-7 days	≤ 4 days	Any time
Bilirubin (mg/dL) Bilirubin (µmol/L)	≥ 2 and < 3 ≥ 34 and <51	≥ 3 and < 5 ≥ 51 and < 85	≥ 5 and < 8 ≥ 85 and < 136	≥ 8 ≥ 136
Bilirubin kinetics			Doubling within 48h	
Transaminases	≤ 2 × normal	> 2 and ≤ 5 × normal	> 5 and ≤ 8 × normal	> 8 × normal
Weight increase	< 5%	≥ 5 % and <10%	≥ 5 % and <10%	≥ 10 %
Renal function	<1.2 × Baseline at transplant	≥ 1.2 and < 1.5 × baseline at transplant	≥ 1.5 and < 2 × baseline at transplant	≥ 2 × baseline at transplant or others signs of MOD/MOF

Patients belong to the category that fulfills 2 or more criteria. If patients fulfill 2 or more criteria in 2 different categories, they must be classified in the most severe category. Patients weight increase ≥ 5 % and <10% is considered by default as a criterion for severe SOS/VOD, however if patients do not fulfill other criteria for severe SOS/VOD, weight increase ≥ 5 % and <10% is therefore considered as a criterion for moderate SOS/VOD.

*In the case of presence of two or more risk factors for SOS/VOD, patients should be in the upper grade.

**Patients with multi-organ dysfunction must be classified as very severe

Mohty M et al. BMT 2016;51:906-912

Management of VOD: a multi-disciplinary approach

- At-risk patients must be identified pre-transplant (team work)
- Nurses play an essential role in assessing and monitoring HSCT recipients
- Early detection is critically important to the overall outcome
- Crucial role of appropriate supportive care

EBMT Consensus (1)

Baseline assessment

- Vital signs
- Baseline weight
- Skin assessment
- Sclera assessment
- Abdomed (manual assessment)
- Abdominal girth (one method)
- RUQ pain
- Liver assessment
- Platelet refractoriness

Suspected VOD (intensification of monitoring)

- **At least 2 times/day**: state of consciuosness; weight, abdominal girth, physical exam, RUQ pain
- **At least 4 times/day**: vital signs, water fluid balance, diuresis, SaO2
- **2 times/day**: CBC for PLT refractoriness
- Daily PT, PTT
- Provideappropriate reassuranceand psychological support to pts and caregivers
- Ensure adequate vascular accesses

Wallhult E et al. - EJH 2016

EBMT Consensus (2)

VOD diagnosed (in addition to actions for suspected VOD)

- Continuous monitoring of vital signs
- Ventilatory support, if necessary (O_2)
- Fluid restriction
- Ensure adequate vascular access
- Careful monitoring of diuresis: bladder catheter, urometer, PS
- Monitoring MOF: cardiac, respiratory and renal function
- Psychological support, arrange for transfer to ICU

Wallhult E et al. EJH 2016

Principles and challenges of VOD managing (prevention and management)

Preventive measures

- Appropriate conditioning regimen selection (risk-adjusted according to HSCT-CI)
- Avoid hepatotoxic drugs during conditioning (azoles, acetaminophen)
- Identify drug-drug interactions in preparative regimens and modify as appropriate
- Pharmacologic monitoring of busulfan
- Avoid the use of progesterone and estrogen if possible
- Aggressive fluid-balance management
- UDCA: recommended by the EBMT and BCSH/BSBMT (combination with defibrotide in high-risk patients?)
- Defibrotide: recommended by the BCSH/BSBMT in high-risk patients
- Unfractioned heparin and LMWH: lack of consistent efficacy → no longer recommended
- Antithrombin not recommended

Dalle J-H et al. BBMT 2016; Wallhult E et al. EJH 2016

Principles and challenges of VOD managing (prevention and management)

Curative measures

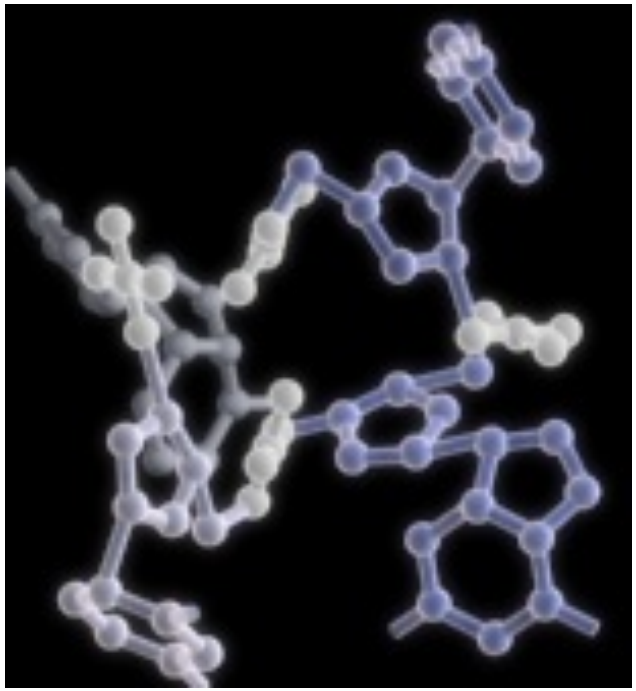
- **Supportive care** must be initiated as soon as possible: fluid and sodium balance, careful use of diuretics, avoidance of hepatotoxic medications (may be challanging, i.e. MTX, CsA)
- **Symptomatic measures**: oxygen therapy, analgesia, paracentesis, thoracentesis, haemodialisys
- **Defibrotide** (approved in EU) 6.25 mg/kg every 6 hours for at least 21 days, to be continued until resolution of the signs and symptoms of VOD
- **High-dose methylprednisolone** may be considered but should be used cautiously due to risk of infection
- rTPA not recommended because of the risk of hemorrhage

Dalle J-H et al. BBMT 2016; Wallhult E et al. EJH 2016

Defibrotide

- Oligonucleotide with:
  - Antiinflammatory
  - Antithrombotic
  - Anti-ischemic activity

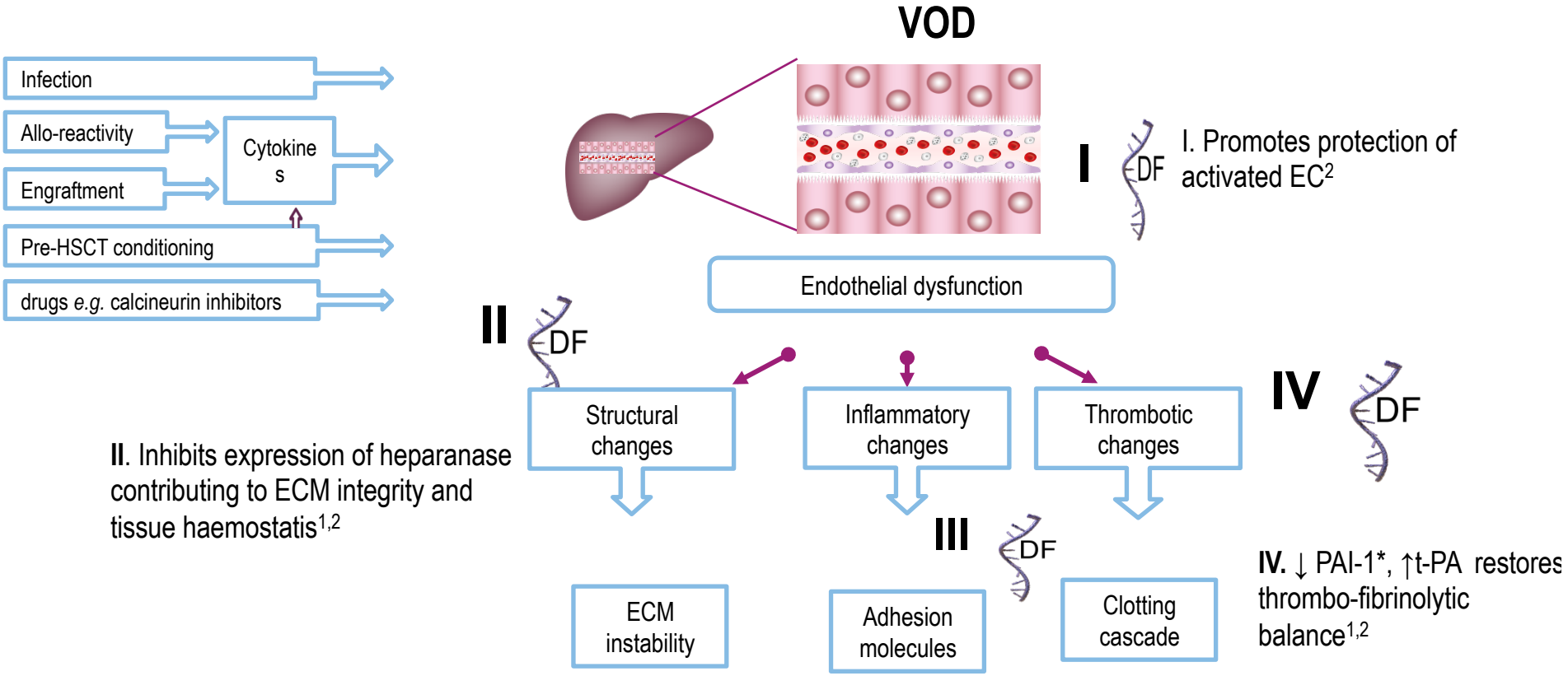
Protective effect on endothelium and restoration of thrombotic-fibrinolytic balance



- Defibrotide in 2014 in European Countries by the EMA for the treatment of severe hepatic VOD in patients undergoing HSCT
  - It is indicated in adults and in adolescents, children and infants over 1 month of age
- The BCSH/BSBMT also recommended defibrotide for the prophylaxis of VOD
- Explored used in GVHD and other endothelial syndromes

BCSH, British Committee for Standards in Haematology; BSBMT, British Society for Blood and Marrow Transplantation; 1. Richardson PG et al. *Expert Opin Drug Saf* 2013;12:123–136; 2. Defitelio® Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002393/WC500153150.pdf, accessed November 2013; 3. Carreras E. Early complications after HSCT. In: Apperley J, Carreras E, Gluckman E Masszi T eds. ESH-EBMT Handbook on Haematopoietic Stem Cell Transplantation. Genova: Forum Service Editore, 2012 pp 176–95; 4. Dignan FL et al. *Br J Haematol* 2013;163:444–457. Mohty et al *BMT* 2015; 781-789

Defibrotide Mechanism of actions



ECM- Extracellular Matrix; EC- Endothelial Cells; PAI- Plasminogen Activator Inhibitor; t-PA- Tissue Plasminogen Activator

1, . Richardson et al. Ther Adv Hematol. 2012; 2. Defibrotide SmPC 2015

TA-TMA: Definition

- Heterogeneous event occurring after HSCT as a result of treatment-related endothelial damage and underlying disease process
- Caused by the aggregation of platelets following exposition to the thrombogenic subendothelial matrix of injured endothelial cells
- Clinical manifestations include destructive thrombocytopenia, microangiopathic hemolytic anemia, ischemic neurological complications and renal dysfunction

TA-TMA: Pathophysiology

- Idiopathic TTP has been attributed to deficient activity of the metalloproteinase responsible for cleaving ultra-large vWF multimers (ADAMTS-13 <5% of normal).
- Unlike classic TTP, patients with TA-TMA have >5% ADAMTS-13 serum activity
- However, recent insights include involvement of complement dysregulation, with possible presence of complement factor H autoantibodies and renal arteriolar C4d deposition
- Recently, an emerging role of renal-centered screening approach has been demonstrated, which utilize the monitoring of blood pressure, urine protein, serum lactate dehydrogenase and hemogram for early detection

Laskin LB et al. Blood 2011, Laskin LB Transplantation 2013, Arai Y et al. BBMT 2013, Kim SS et al. Transfusion 2014; Jodele S et al. 2015; Elsallabi et al. Thromb Hemost 2016

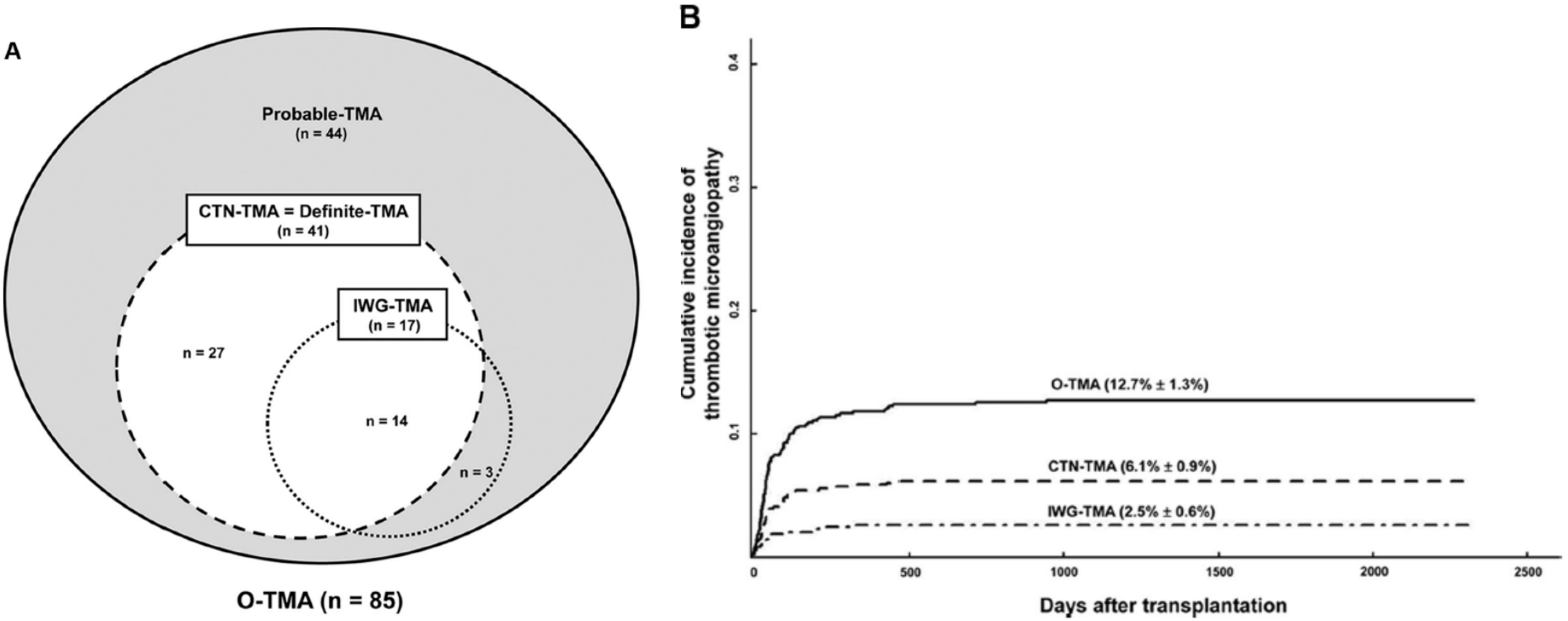
TA-TMA: Diagnostic criteria

Clinical/laboratory findings	BMT-CNT criteria	IWG-EBMT criteria	O-TMA criteria
Schistocytosis	>2 HPF on peripheral smear	>8 HPF on peripheral smear	>2 HPF on peripheral smear
↑ LDH	yes	Yes	Yes
Thrombocytopenia (PLT< $50x10^9$/l)	-	Yes	Yes
Anemia	-	Yes	Yes
↓ Haptoglobin	-	Yes	Yes
Negative antiglobulin test	Yes	-	Yes
Renal failure +/- CNS involvement	Yes	-	-

BMT-CTN criteria (Bone Marrow Transplant Clinical Trials Network), *Ho VT. BBMT 2005*
IWG-EBMT criteria (International Working Group of the EBMT), *George JN. Transfusion 2004*
O-TMA criteria (Overall-TMA), *Cho BS. Transplantation 2010*

Modified from Kim SS. Transfusion 2014

TA-TMA: Diagnostic criteria



Cho BS et al. Transplantation 2010

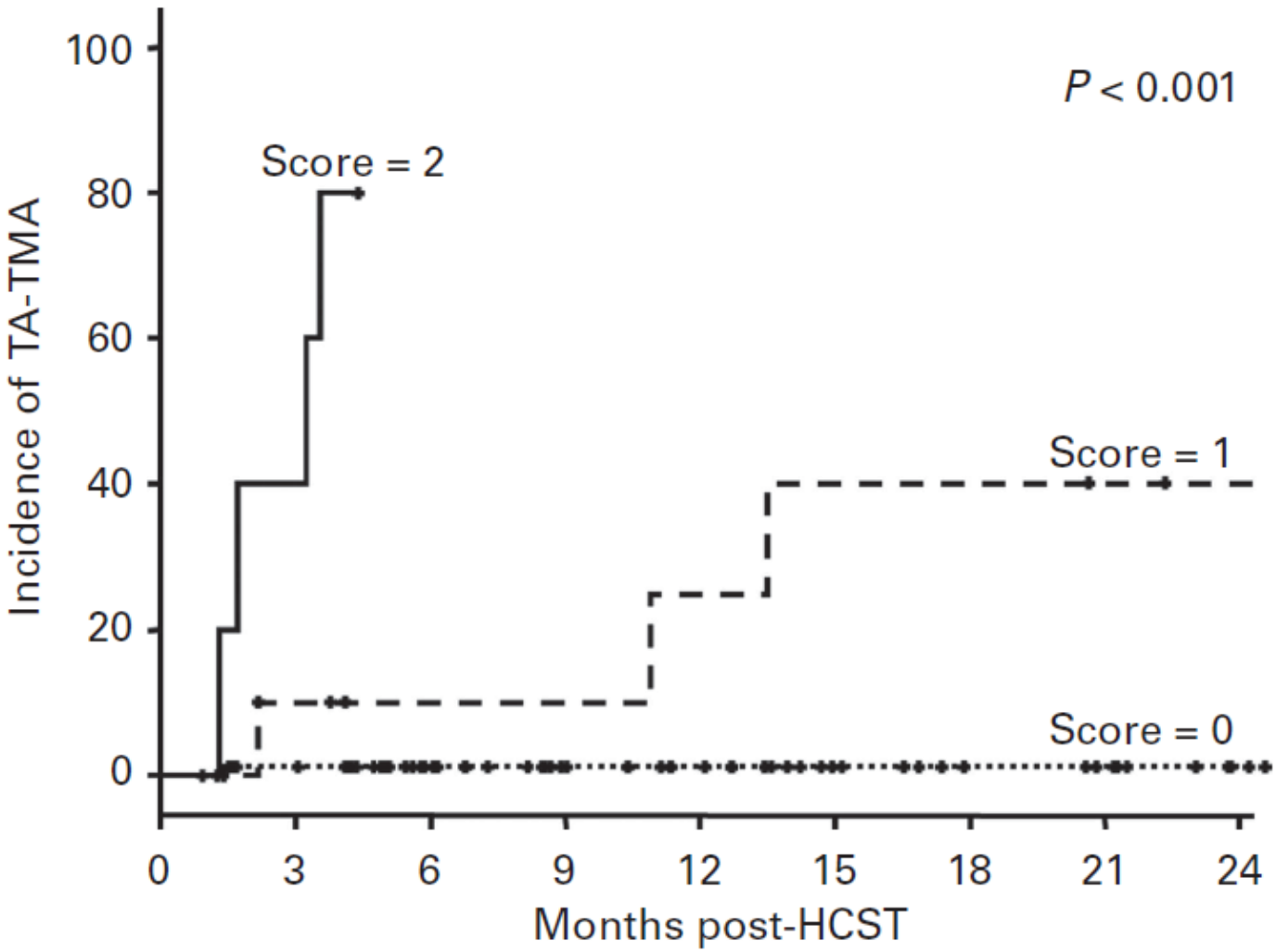
TA-TMA: Risk factors

Table 4.

Variab

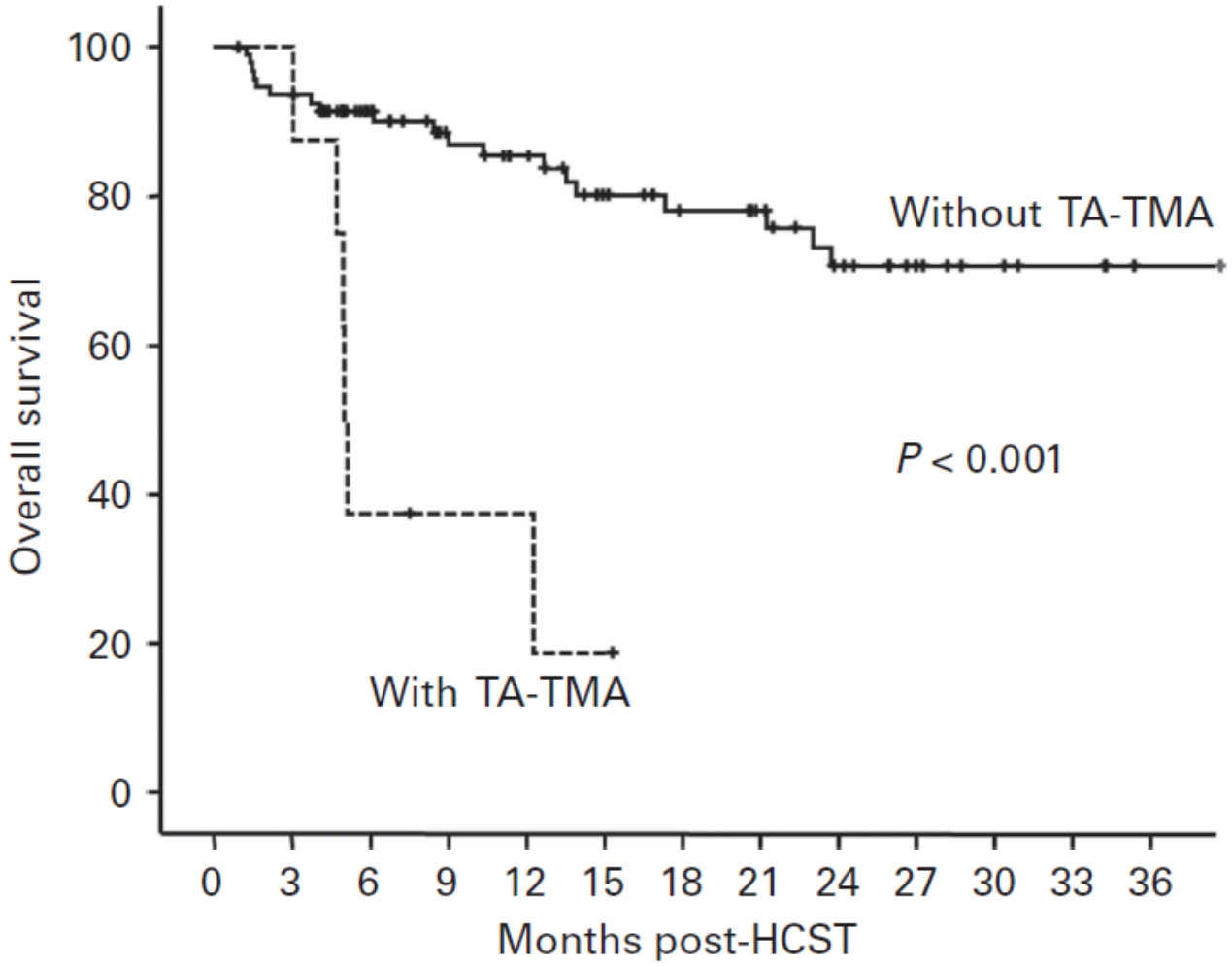
Lympl
Advar
Prior a
Prior H
or allo
Use o
FLU +
Use o
Grade
Serum
Toxic
Invasi

Abbrev
transpl
ditionir



Labrador J et al BMT 2014

TA-TMA and Survival



Cause of death:

Infections (fungal and viral)
GVHD
DAH
VOD
Hemorrhages

Labrador J et al BMT 2014

TA-TAM: Management

- No standard treatment exists
- Plasma exchange → not clearly efficacious
- Remove triggering agent:
- CNI → MMF + steroids
- Not efficacious: steroids, heparin, fibrinolitics, trombolitics, iv Igs, splenectomy
- Reports on use of: rituximab, daclizumab, defibrotide

Engraftment syndrome (ES)

Generally occurring within 96 hours from engraftment

Cause: release pro-inflammatory cytokines, products of degranulation and oxidative metabolism → endothelial damage

Risk factors

- Growth factors
- PBSC
- High number HSC infused
- Autologous SCT

EBMT Handbook ed 2012; Carreras BMT (2010) 45, 1417

Engraftment syndrome (ES)

Clinical manifestations:

- Mainly post-auto SCT
- Non infectious fever (>38 w/o clinical-microbiological evidences) → 98-100%
- High CRP → 100%
- Skin rash mimicking aGVHD > 25% BSA → 56%-65%
- Hepatic disfunction (bili, AST/ALT) → 20-70%
- Pulmonary infiltrates → 11-37 %
- Diarrhea → 11-40%
- Renal disfunction → 26%
- Weight gain, edema , ascites → 20%

EBMT Handbook ed 2012
Carreras BMT (2010) 45, 1417
Lopes da Silva, BMT (2012) 47, 456
Schmid, BBMT (2008) 14:438

Engraftment syndrome (ES)

Treatment:

- Stop G-CSF
- MPD 1 mg/kg for 3 days, taper over 7-8 days
- Broad spectrum antibiotic therapy

Prognosis

Complete resolution >80% cases


Thank you!