ER Congressi

Leucemie Acute Linfoblastiche
Policlinico S. Orsola-Malpighi
Bologna, 13 maggio 2016

VOD E TRAPIANTO ALLOGENICO: QUALI STRATEGIE TERAPEUTICHE?

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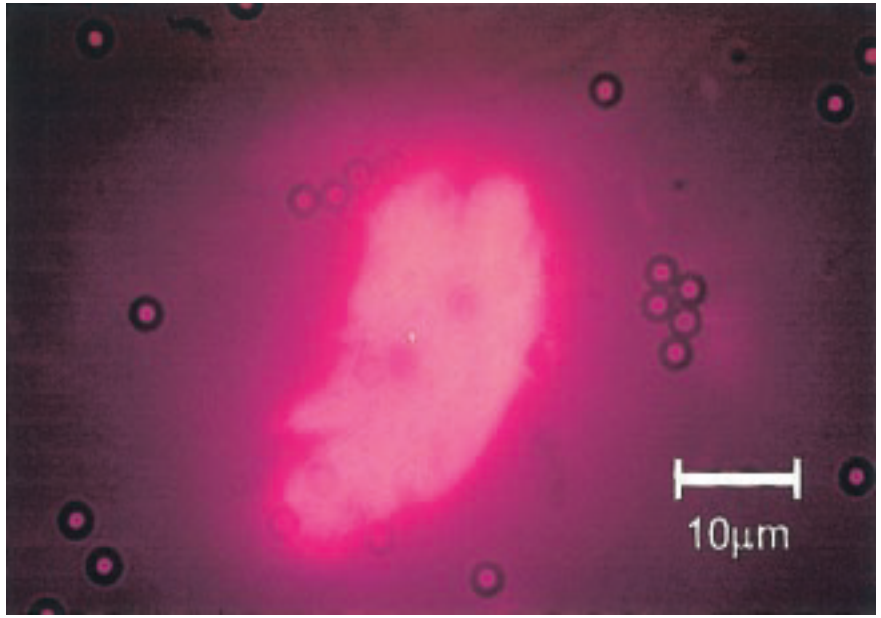
Fisiopatologia e patogenesi del danno endoteliale nel post-trapianto

Che i pazienti sottoposti a Trapianto Allogenico di Cellule Staminali siano esposti, sia per la pregressa terapia sia per condizioni fisiopatologiche intrinseche del TCSE, ad un danno endoteliale diffuso è cosa nota. Certamente più complesso è riconoscere, partendo da questo assunto, il contributo di questo danno nella patogenesi di molte complicanze cliniche trapianto correlate.



Circulating endothelial cell from a patient undergoing hematopoietic stem cell transplantation: immunomagnetic isolation and subsequent rhodamine-coupled UEA-1 stain. Note that several Dynabeads are attached to the cell and that the cytoplasm shows homogenous staining for UEA-1.

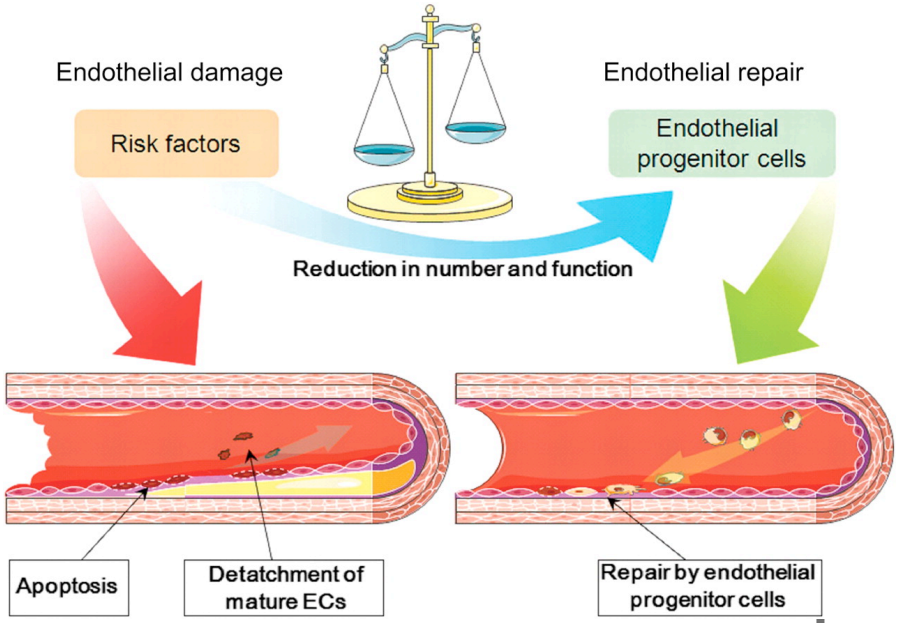
Woywodt et al Blood 2004

Fisiopatologia e patogenesi del danno endoteliale nel post-trapianto

L'endotelio va considerato globalmente come un organo a tutti gli effetti altamente attivo a livello metabolico ed endocrino. Produce infatti una moltitudine di differenti molecole, inclusi ormoni vasoattivi peptidici, fattori di crescita, fattori della coagulazione e molecole di adesione.

È un'interfaccia biologica attiva tra sangue e tessuti che regola il delicato equilibrio tra:

- Vasocostrizione e vasodilatazione
- Coagulazione e fibrinolisi
- Proliferazione ed apoptosi
- Adesione e diapedesi dei leucociti nel sangue



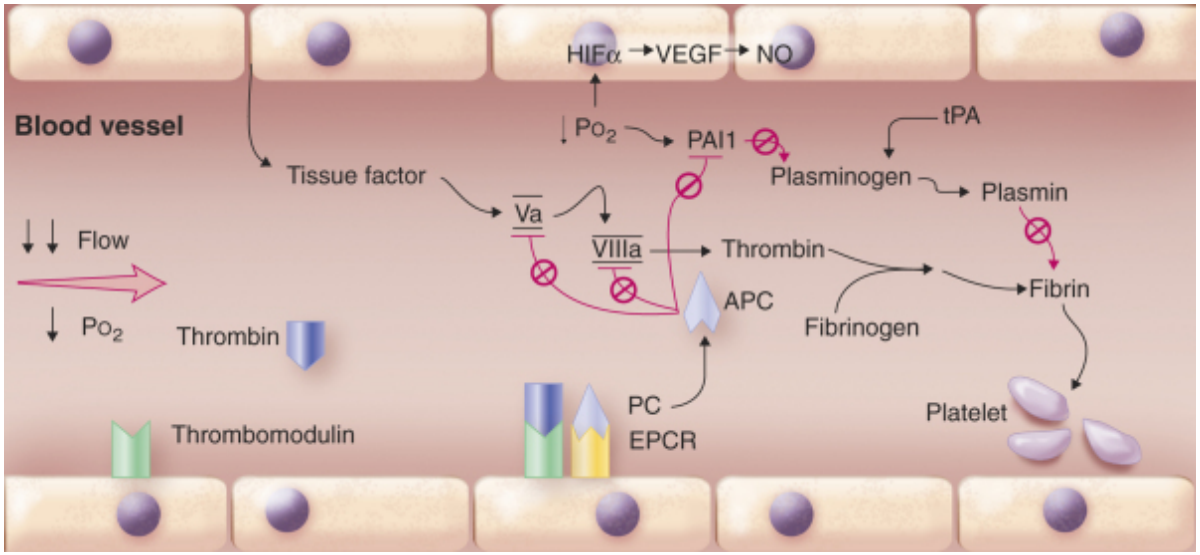
Fisiopatologia e patogenesi del danno endoteliale nel post-trapianto

- Stato pro-coagulante e ipo-fibrinolitico
- Alterazione della permeabilità capillare

- Risposta pro-infiammatoria e attivazione delle cellule T del donatore

Stato pro-coagulante e ipo-fibrinolitico

- Induzione espressione fattore tissutale, deposizione di fibrinogeno
- Aumento livelli di PAI-I, trombopoietina e fattore di von Willebrand
- Consumo di AT-III, proteina C, fattore VII



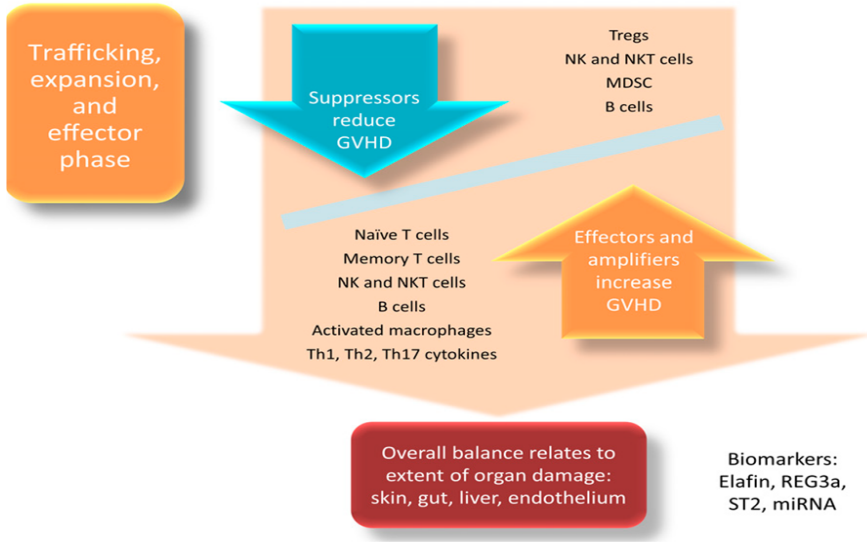
Durante l'erogazione della chemio-radioterapia del regime di condizionamento si accumulano I metaboliti tossici (prvalentemente di CY post BU) nello spazio sinusoidale della zona 3 dell'acino epatico.

Risposta pro-infiammatoria e attivazione delle donor T-cells

Differenti stimoli irritativi concomitanti nel post-HSCT (irradiazione, rilascio di LPS e TNFa, mucosite) contribuiscono a determinare il rilascio di citochine pro-infiammatorie ed il richiamo di effettori dell'immunità innata.

- IL-6, IL-8, IL-12
- IL-1
- richiamo e attivazione neutrofili e macrofagi tissutali

L'endotelio danneggiato non costituisce più una barriera di separazione tra linfociti del donatore e cellule presentanti l'antigene e quindi favorisce la attivazione degli stessi.



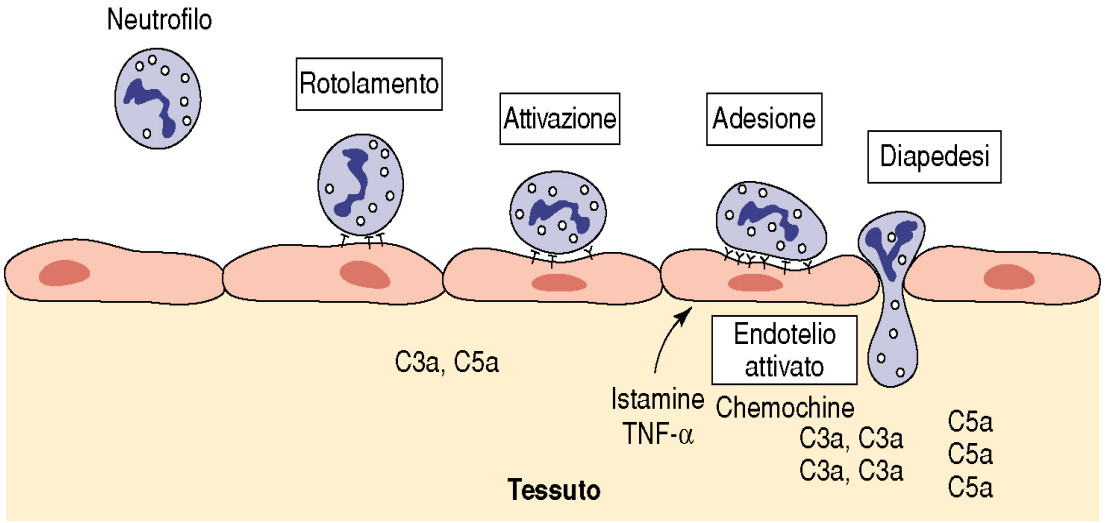
In seguito all'attivazione endoteliale si producono citochine pro-infiammatorie ed eparanase e si alterano le molecole di adesione
Questo determina una alterazione della struttura del citoscheletro che porta ad una aumentata permeabilità facilitando la fuoriuscita di globuli rossi e leucociti nello spazio di Disse così da portare ad una iniziale ostruzione sinusoidale.

Alterazione della permeabilità capillare

La attivazione delle cellule endoteliali determina:

- l'iperespressione di molecole di adesione (p-selectina, e-selectina, ICAM-1 e VCAM-1)
- modificazione conformazionale del citoscheletro delle cellule endoteliali.

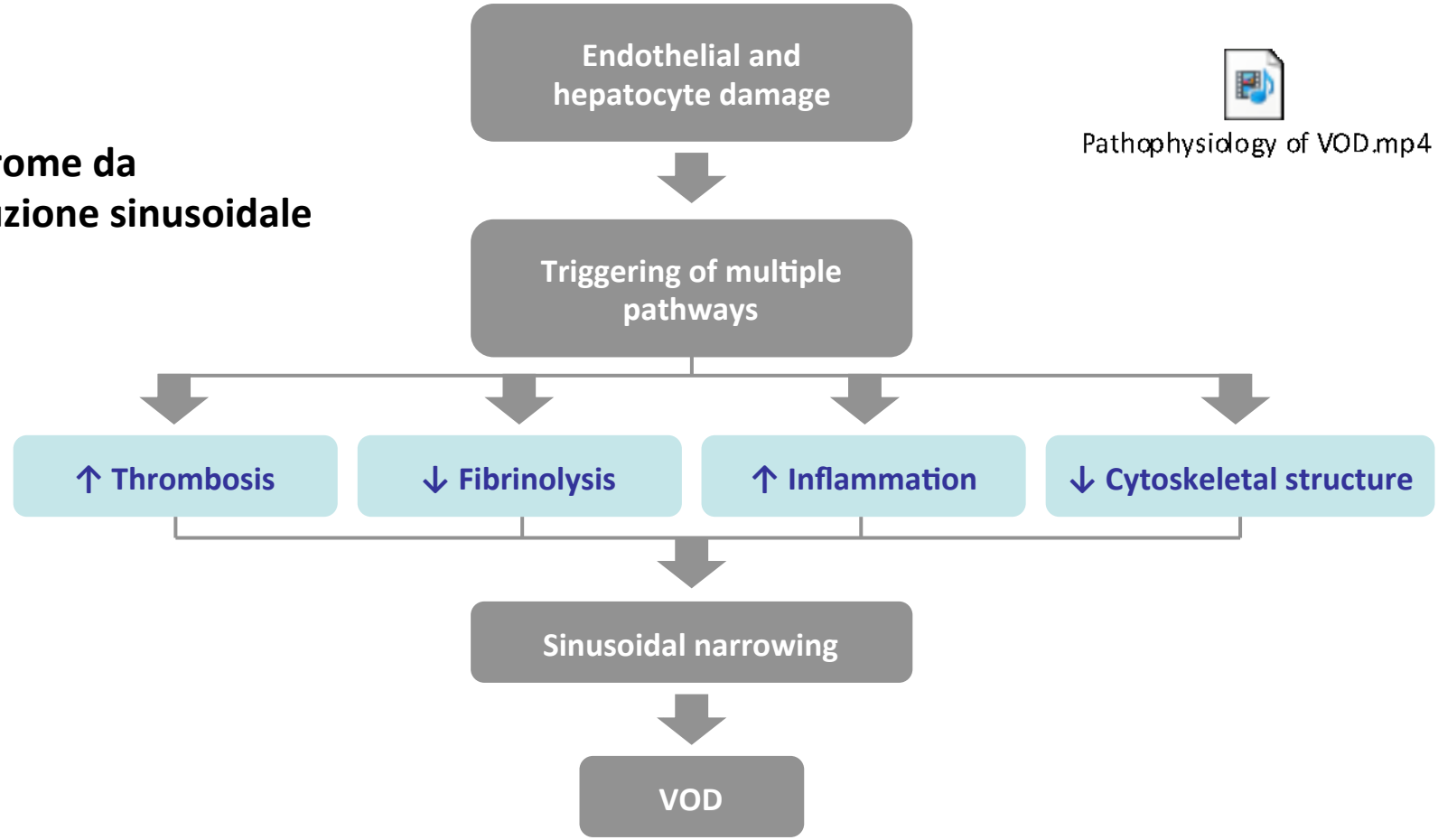
Adesione e diapedesi di leucociti



L'aumento di TF e PAI-1 (che inibisce t-PA) determina l'innesco di uno stato pro-trombotico ed iperfibrinolitico. Questo contribuisce alla formazione del coagulo che aumenta ulteriormente la pressione trans-sinusoidale ed ostruisce definitivamente il sinusoide.

Fisiopatologia e patogenesi del danno endoteliale nel post-trapianto

Sindrome da ostruzione sinusoidale



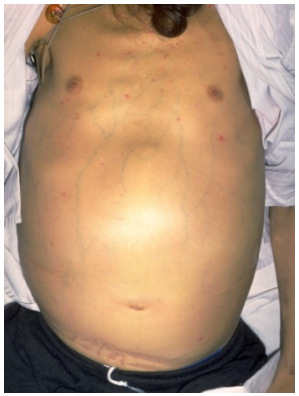
Pathophysiology of VOD.mp4

E' importante riconoscere precocemente segni e sintomi della VOD [1-3]

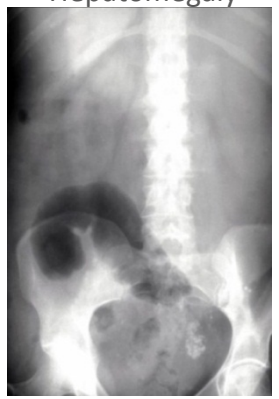
- Segni e sintomi di VOD si verificano tipicamente nei primi 35-40 giorni dal TMO ma possono presentarsi anche dopo [1-3]
- Segni e sintomi possono essere eterogenei ed essere espressione di altre complicanze [3]
- Gli indicatori di VOD includono: [3]
  - Ritenzione idrica
  - Ascite
  - Ittero
  - Tendenza all'epatomegalia
  - Incremento ponderale
  - Edemi
  - Dolore al quadrante superiore destro
  - Trombocitopenia
  - MOF

Sintomi Precoci

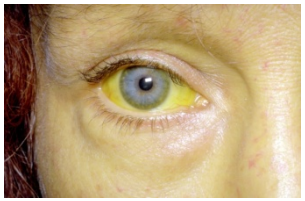
Ascites



Hepatomegaly



Jaundice



Symptoms of VOD usually occur up to 35-40 days following HSCT,[1] although later onset has been reported (21–508 days[2])

VOD: Hepatic veno-occlusive disease; HSCT: Haematopoietic stem cell transplantation; MOF: Multi-organ failure

1. Richardson PG et al. *Ther Adv Hematol* 2012;3:253–265. **2.** Hasegawa S et al. *Bone Marrow Transplant* 1998;22:1191–1197. **3.** Carreras E. Early complications after HSCT. In: *EBMT-ESH Handbook* 2012:177–195. Images available (from left to right) at: http://tinyurl.com/ppa4on9; http://tinyurl.com/pk9j4fs; http://tinyurl.com/ns8e7y7; accessed September 2013

DEF/EUR/024/0214-01 Date of preparation: February 2014

THINK VOD: FOREWARNED IS FOREARMED

- The disease course of VOD is unpredictable and can progress rapidly.[1,2] If left untreated, sVOD has a mortality rate of ≥80%[3]
- Daily monitoring is essential to detect early signs and symptoms of VOD[4]
- As part of daily physical examinations, look for warning signs of VOD

If a patient has any of these warning signs

Rapid weight gain

Rising bilirubin

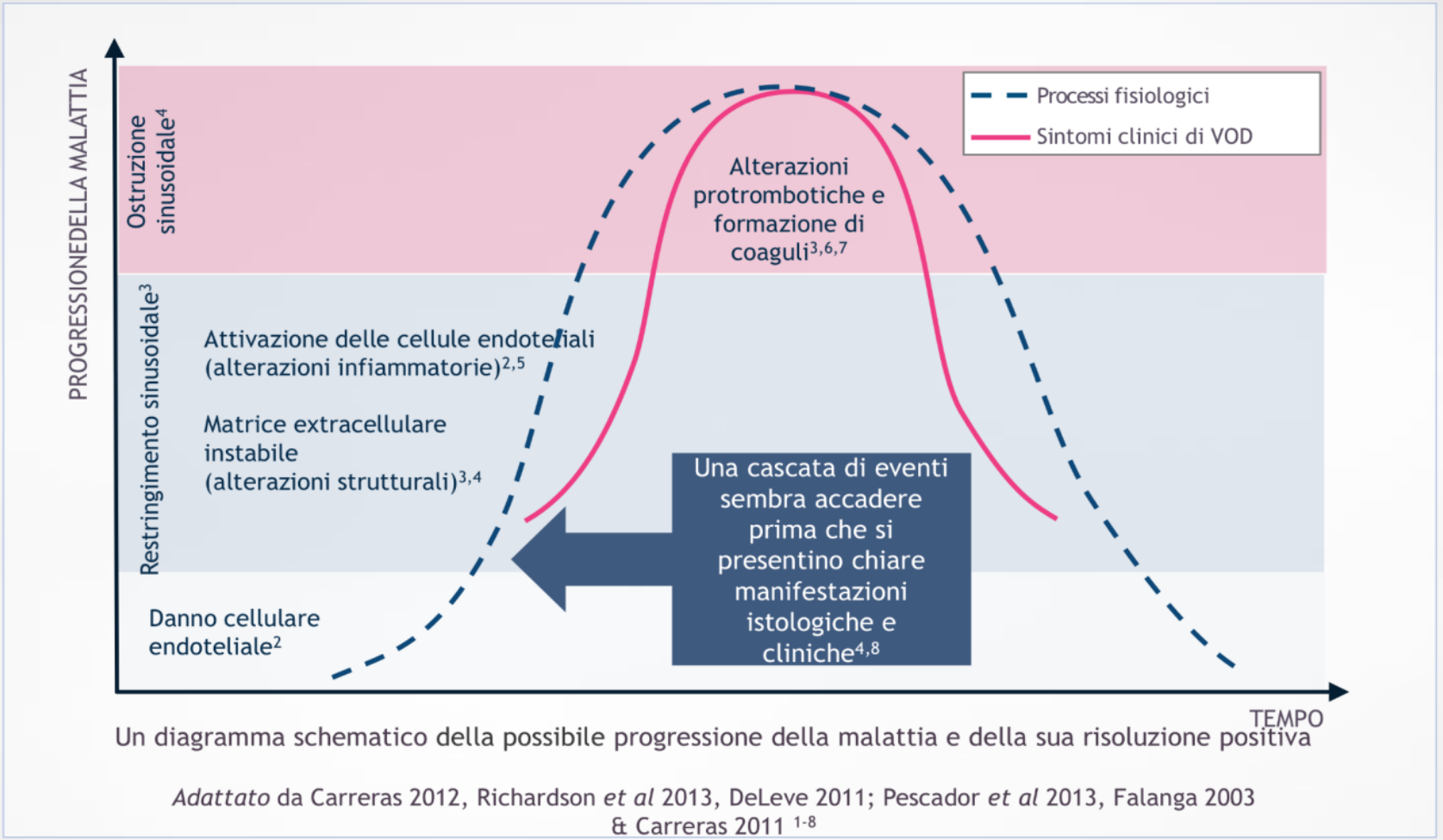
S VOD S

Tender hepatomegaly

Urgently rule out VOD

[1]Schoppmeyer K, et al. *Z Gastroenterol* 2006;44(6):483–486. [2]Dalle J-H, Giralt SA. *Biol Blood Marrow Transplant* 2015 (Epub ahead of print).
[3]Coppell JA, et al. *Biol Blood Marrow Transplant* 2010;16(2):157–168. [4]Carreras E. *Br J Haematol* 2015;168(4):481–491.

La progressione della malattia è imprevedibile[1]



Un diagramma schematico della possibile progressione della malattia e della sua risoluzione positiva

Adattato da Carreras 2012, Richardson *et al* 2013, DeLeve 2011; Pescador *et al* 2013, Falanga 2003 & Carreras 2011 [1-8]

VOD, malattia veno-occlusiva

1. Schoppmeyer K, et al. Z Gastroenterol 2006; 44(6): 483–486. 2. Carreras E. Chapter 11: Early complications after HSCT. EBMT-ESH Handbook 2012: 176–195. 3. Richardson PG, et al. Biol Blood Marrow Transplant 2013; 19: S88–90. 4. DeLeve LD, et al. Vascular Liver Disease and the Liver Sinusoidal Endothelial Cell. Vascular Liver Disease: Mechanisms and Management. New York: Springer, 2011: 25–40. 5. Pescador R, et al. Cardiovasc Drug Rev 2000; 18(4): 304–311. 6. Baron F, et al. Haematologica 1997; 82: 718–725. 7. Falanga A. Leukemia. 2003; 17: 1636–1642;; 8.Carreras E and Diaz-Ricart M. Bone Marrow Transplant 2011; 46: 1495—1502

CLASSIFICAZIONE PROGNOSTICA (sec. Mc Donald '93) [1,2]

Gravità della VOD	Sintomi
Lieve	• Auto-limitante • Non richiede trattamento
Moderata	• Evidenze di danno epatico • Richiede trattamento (analgesici, diuretici e altre terapie di supporto) • Solitamente si ha la guarigione dei pazienti
Grave	• Mancata risoluzione dei sintomi o decesso prima di 100 giorni dopo HSCT • Insufficienza multiorgano, grave iperbilirubinemia con rapido aumento di peso

1. DeLeve LD et al. *Hepatology* 2009;49:1729-1764; 2. McDonald GB et al. *Ann Intern Med* 1993;118:255–267

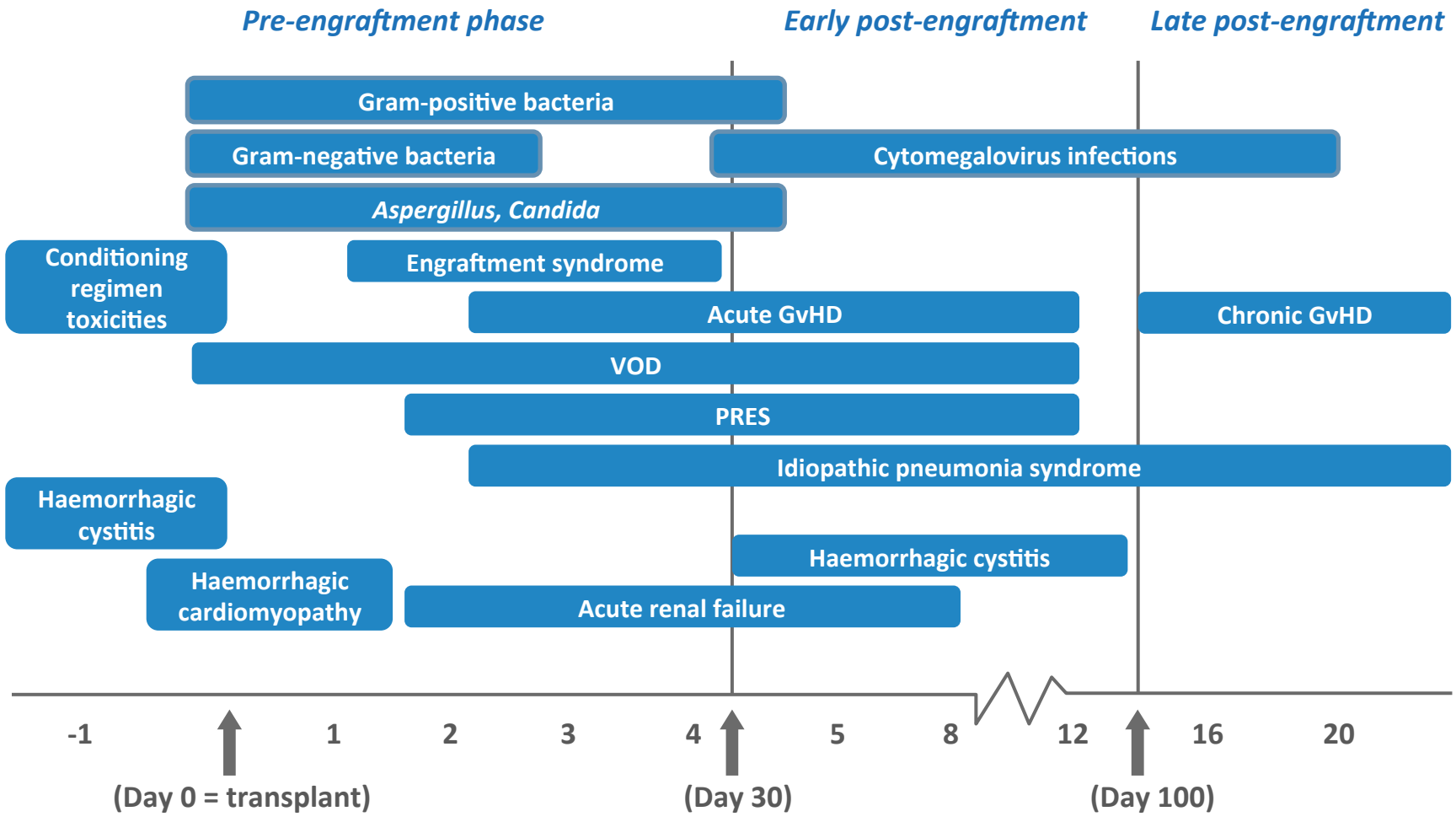
OVERLAPPING CLINICAL MANIFESTATIONS IN VASCULAR ENDOTHELIAL CELL SYNDROMES[1–3]

	VOD[1]	Capillary leak syndrome[2]	Engraftment syndrome	Diffuse alveolar haemorrhage	Idiopathic pneumonia syndrome	Transplant-associated microangiopathy[2]	Liver/GI graft versus host disease[3]
Fever		✓	✓		✓	✓	
Jaundice	✓						✓
Hepatomegaly	✓						
Weight gain	✓	✓	✓				
Oedemas	✓	✓					
Ascites	✓	✓					
Lung infiltrates	✓	✓	✓	✓	✓		
Dyspnoea	✓	✓	✓	✓	✓		
Hypoxia	✓	✓	✓	✓	✓		
Diarrhoea			✓				✓
Renal dysfunction	✓	✓	✓			✓	
Neurological dysfunction			✓			✓	
Evolution to MODS	✓	✓	✓		✓	✓	

Adapted from Carreras E and Diaz-Ricart 2011[2] and Apperley J and Masszi T in EBMT-ESH Handbook 2012[3]

[1]Carreras E. Chapter 11: Early complications after HSCT. EBMT-ESH Handbook 2012:176–195. [2]Carreras E and Diaz-Ricart M. *Bone Marrow Transplant* 2011;46:1495–1502.
[3]Apperley J, Masszi T. Chapter 13: Graft-versus-host disease. EBMT-ESH Handbook 2012:216–233.

Fisiopatologia e patogenesi del danno endoteliale nel post-trapianto



UNDERSTANDING RISK FACTORS IS IMPORTANT[1,2]

Transplant-related factors[3]

Pre-transplant patient characteristics[3]

[1]Mohty M, et al. *Bone Marrow Transplant* 2015;50:781–789. [2]Carreras E, *Br J Haematol* 2015;168(4):481–491.
[3]Dalle J-H, Giralt SA. *Biol Blood Marrow Transplant* 2015 (Epub ahead of print).

IDENTIFICATION OF SPECIFIC RISK FACTORS CAN HELP GUIDE TREATMENT DECISIONS[1]

- These risk factors may affect patients of all ages, although they may have been identified initially in either paediatric or adult populations[1]

Risk factor[1]	OR <3
Peripheral blood SCT versus BMT	1.3
Unrelated donor/HLA mismatch	1.4
Acute hepatic/gut GvHD	~2.0
Non-T cell-depleted grafts	2.2
>12 months between diagnosis & transplantation	2.3
High-dose total body irradiation	2.8
Allogeneic versus autologous SCT	2.8

Risk factor[1]	OR = 3–10
GvHD prophylaxis	3–4.2
High-dose/myeloablative therapy	2.3–7.9

Adapted from Dalle J-H, Giralt SA 2015[2]

OR = Odds ratio for developing VOD, compared with odds when not exposed to the risk factor.

[1]Dalle J-H, Giralt SA. *Biol Blood Marrow Transplant* 2015 (Epub ahead of print).

PATIENT-RELATED RISK FACTORS ARE IMPOSSIBLE TO REVERSE[1]

Risk factor[2]	OR <3
Underlying myelodysplasia	1.5
Inborn errors of metabolism	1.8
Prior SCT	1.9
Underlying leukemia (CML)	2.2 (3.0)
Vancomycin during cytoreductive therapy	2.4
Impaired pulmonary function	2.4
Poor performance status (Karnofsky score <90%)	2.7
Abdominal radiation	2.9

Risk factor[2]	OR = 3-10
Fever/parenteral nutrition/ diarrhoea prior to transplant	2.9/3.0/ 3.2
Ferritin levels >1000 ng/mL	3.1
Underlying immunodeficiency	3.3
Pre-existing liver disease	3.4
Underlying thalassemia	4.0
Sepsis	4.1
Genetic factors (GSTM1 null genotype)	4.1
Increased transaminase levels	2.4–4.6
Pretransplant acyclovir	4.8
Age	5.2–9.5

Risk factor[2]	OR >10
Treatment with norethisterone	10.1
Treatment with gemtuzumab ozogamicin	19.8
Bilirubin >26 µmol/L before BMT	23.5

Adapted from Dalle J-H, Giralt SA 2015[2]

OR = Odds ratio for developing VOD, compared with odds when not exposed to the risk factor.

[1]Mohty M, et al. *Bone Marrow Transplant* 2015; 50:781–789. [2]Dalle J-H, Giralt SA. *Biol Blood Marrow Transplant* 2015 (Epub ahead of print).

VOD: Summary

- DIAGNOSI PRECOCE
- CORRETTA DIAGNOSI DIFFERENEZIALE
- T E M P E S T I V I T A' E D A D E G U A T E Z Z A DELL'INTERVENTO TERAPEUTICO
- DISPONIBILITA' DI PRESIDI TERAPEUTICI EFFICACI

Diagnosis of VOD is a two-stage process which excludes diseases that may mimic VOD [1,2]

1. Fulfilment of diagnostic criteria

Modified Seattle criteria	Baltimore criteria

• Presentation before Day 20 post-HSCT of two of the following:
  • Bilirubin >2 mg/dL (>34 µmol/L)
  • Hepatomegaly or right upper quadrant pain
  • Weight gain (>2% basal weight)
	• Bilirubin level >2 mg/dL (>34 µmol/L) before Day 21 post-HSCT and at least two of the following:
	  • Painful hepatomegaly
	  • Ascites
	  • Weight gain (≥5% basal weight)

2. Exclusion of other conditions that may mimic symptoms of VOD by differential diagnosis

Conditions that may mimic VOD		
• Acute liver graft-versus-host disease • Fungal infiltration of the liver • Viral hepatitis • Cholangitis lenta,* e.g. during sepsis	• Drug-induced liver disease • Constrictive pericarditis and right congestive heart failure • Persistent tumour infiltration of the liver	• Pancreatic ascites and chylous • Ascites • Parenteral nutrition • Haemolysis • Renal failure

* 'Cholangitis lenta' is an old entity that describes a form of chronic sepsis associated with biliary tract inflammation and hyperbilirubinaemia in the absence of demonstrable extrinsic obstruction.

1.Carreras E. Early complications after HSCT. In: *EBMT-ESH Handbook* 2012:177–195. **2.** Helmy A. *Aliment Pharmacol Ther* 2006;23:11–25 **2.** Helmy A. *Aliment Pharmacol Ther* 2006;23:11–25

DEF/EUR/024/0214-01 Date of preparation: February 2014

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

This grading system is divided into 5 categories, as in the Common Terminology Criteria for Adverse Events (CTCAE):

- grade 1 = mild
- grade 2 = moderate
- grade 3 = severe
- grade 4 = very severe and
- grade 5 = death.

Mohty et al., Bone Marrow Transplant 2016 in press

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

*** Time from the date when the first signs/symptoms of SOS/VOD began to appear (retrospectively determined) and the date when the symptoms fulfilled SOS/VOD diagnostic criteria

New EBMT Criteria Summary

- Categorization of mild, moderate, severe, very severe-MOD/MOF
- Rather than based on feeling and only clinical symptoms, they will be based on more objective measurable parameters, i.e.
    - Transaminases
    - Bilirubin incl. kinetics
    - Will include the chronology of onset of VOD
- Symptoms can occur even late, day +21 is no longer the cut-off
- Better characterization of severe VOD/SOS cases
    - It's downgrading the severity of 'severe'

Proposed new diagnostic criteria for paediatric patients currently under consideration

Purpose:

Early, preliminary diagnosis and early therapeutic/preemptive intervention

Proposed paediatric diagnostic criteria (presence of ≥2 parameters):

1. **Unexpected refractoriness to platelets transfusions***
2. **Unexpected weight gain on 3 consecutive days or weight gain >5% *vs* baseline (despite use of diuretics)**
3. **Hepatomegaly (US confirmed) *vs* baseline**
4. **Ascites (US confirmed) *vs* baseline**
5. **Rising bilirubin from an individual baseline**

Pre-requisite: All patients need to have baseline US prior to SCT

NO 20 or 21 days limitation!

*** ≥1 PLT TF/day to maintain institutional transfusion criteria**

courtesy of S. Corbacioglu; EBMT 2016

Malattia Veno Occlusiva del Fegato
Tecniche diagnostiche

Criteri morfologici

Misura del fegato (asse verticale)
Misurazione della milza
Ispessimento della parete colecistica (≥6 mm) (sens. 65% spec. 95%)
Diamentro Vena Porta ingrandito (≥8 mm)
Diametro Vena Epatica ridotto (<3mm) (sens. 64% e spec. 93%).
Ascite
Visualizzazione della Vena periombelicale, indice di ipertensione portale severa

Criteri Doppler

Flusso portale rallentato (vel max 10 cm/sec) o flusso epatofugo
Flusso nella vena periombelicale (epatofugo) registrabile nella vena ricanalizzata

Studio emodinamico per via trans-giugulare o femorale permette di misurare il gradiente pressorio venoso epatico (HVPG)

Biopsia per via transparietale

Fattori biologici: Incremento di PAI-1

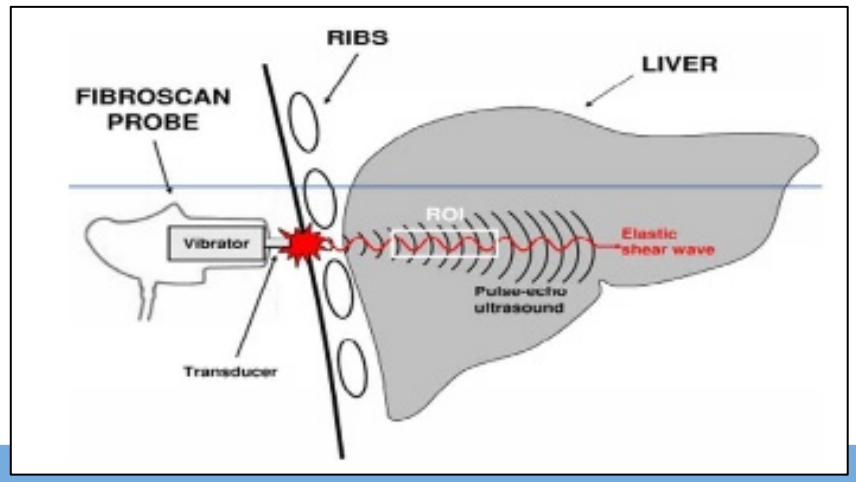
Linee guida British Society for Blood and Marrow Transplantation[1]:

- Utilizzo dei criteri modificati Seattle o Baltimore (1A)
- Utilizzo dell'*imaging* (ecografico) nella diagnosi differenziale (1C)
- La biopsia epatica può essere riservata nei casi dubbi o per esclusione di altre patologie (1C)
- La valutazione di PAI-1 non rientra nel normale work-up clinico (2C)

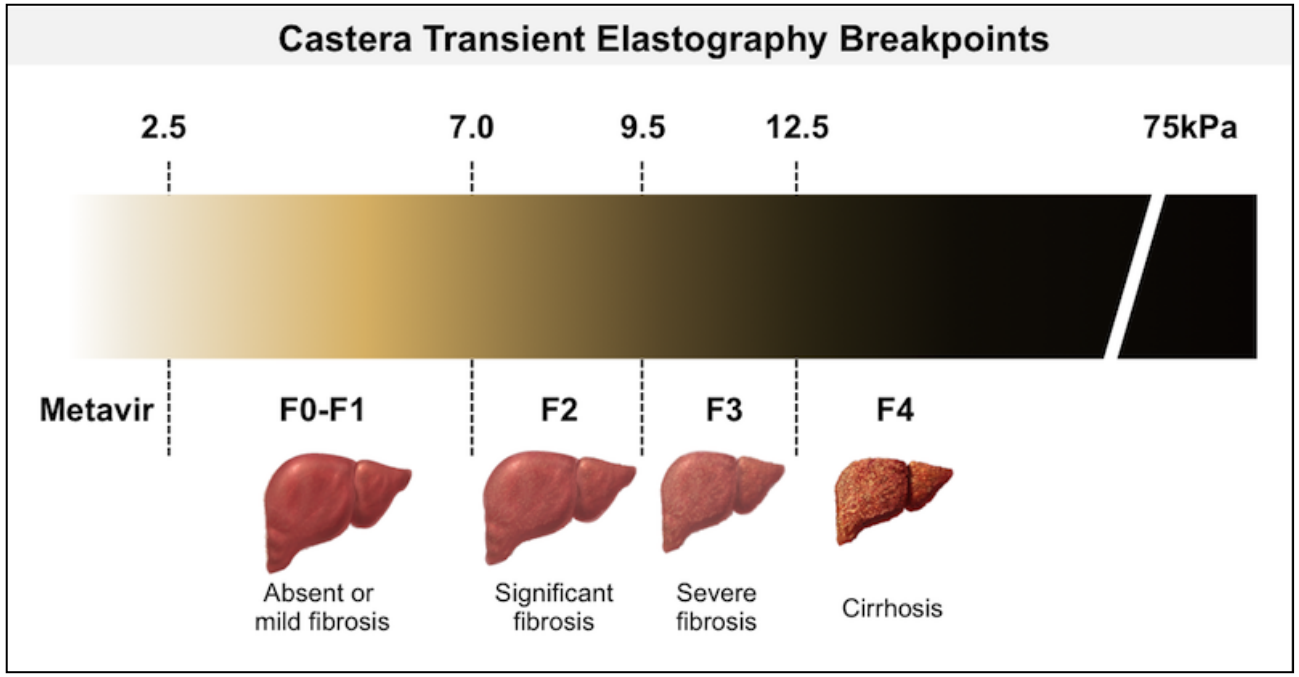
Elastografia epatica (Fibroscan®)

Elastografia epatica (Fibroscan®)

Il concetto fisico della TE è basato sul principio che la velocità di propagazione di un'onda è proporzionale alla "stiffness" (rigidità) del tessuto.
-> più è rigido il tessuto, più veloce è la propagazione dell'onda.
Per misurare la "liver stiffness" (LS), una sonda ecografica è montata sull'asse di un vibratore che viene posizionato sopra il fegato. Il vibratore emette delle vibrazioni a bassa frequenza, e la velocità di propagazione delle onde attraverso il parenchima epatico viene misurata tramite l'acquisizione di un segnale ecografico.
La LS viene misurata in un volume cilindrico di circa 1 x 4 cm, che deve essere a distanza di circa 25-65 mm dalla superficie corporea. I risultati sono immediatamente disponibili e vengono espresso in kilopascals (kPa) su una scala da 2.5 – 75 kPa (valore normale intorno a 5 kPa).



Elastografia epatica (Fibroscan®)



Karlas et al. Value of liver elastography and abdominal ultrasound for detection of complications of allogeneic hemopoietic SCT. *Bone Marrow Transplant.* 2014

Utilità della TE per:

- Rilevazione del grado di fibrosi epatica
- Monitoraggio dell'ipertensione portale

- **Caratterizzazione dello stato di necro-infiammazione e/o colestasi del tessuto epatico anche in assenza di fibrosi**

Predizione di tossicità epatica post-TCSE?

Baseline examination	Sens %	Spec %	AUC	Cutoff	PPV	NPV
TE	53.8	86.8	0.635	>5.7	58.3	84.6

VOD: Summary Diagnosis

•It is recommended that the diagnosis of veno-occlusive disease (sinusoidal obstruction syndrome) be based primarily on established **clinical criteria** (modified Seattle or Baltimore criteria) (1A)

•**Ultrasound imaging** may be helpful in the exclusion of other disorders in patients with suspected veno-occlusive disease (sinusoidal obstruction syndrome) (1C)

•It is recommended that **liver biopsy be reserved** for patients in whom the **diagnosis** of veno-occlusive disease (sinusoidal obstruction syndrome) is unclear and there is a need to exclude other diagnoses (1C)

•It is recommended that liver biopsies are undertaken using the **transjugular approach** in order to reduce the risks associated with the procedure (1C)

Dignan FL 2013

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for prophylaxis of hepatic veno-occlusive disease in people undergoing haematopoietic stem cell transplantation (Review)

Cheuk DKL, Chiang AKS, Ha SY, Chan GCF

Key Results

Ursodeoxycholic acid may reduce the occurrence of VOD, deaths from all causes and deaths due to VOD, but there was no evidence of a difference in overall survival. There was no evidence of difference in occurrence of VOD between treatment and control groups for heparin, LMWH, defibrotide, glutamine, FFP, antithrombin III, between heparin and LMWH, between heparin and PGE1, and between LMWH and PGE1. There was no evidence of difference in survival between treatment and control groups for heparin and defibrotide. There were no data on survival for trials of LMWH, glutamine, FFP, antithrombin III, between heparin and LMWH, between heparin and PGE1, and between LMWH and PGE1. There were no data on quality of life for any trials. Eleven trials reported adverse effects. There was no evidence of a difference in adverse events among treatment groups, except for one trial showing that defibrotide resulted in more adverse events compared with no treatment.

Quality of the Evidence

The quality of evidence for all outcomes was low to very low, because of high risk of bias in study design, results inconsistent across studies and imprecision of results.

Conclusion

There is low or very low quality evidence that ursodeoxycholic acid may reduce the incidence of hepatic VOD, overall mortality and mortality due to VOD in people undergoing HSCT. However, the most effective treatment is not well-defined. There is insufficient evidence to support the use of heparin, low molecular weight heparin, defibrotide, glutamine, FFP, antithrombin III, and prostaglandin E1. Further high-quality research is needed.

Terapia

1. **Terapia di supporto**
   a) Diuresi forzata per la riduzione della ritenzione idrica, mantenendo però una perfusione renale adeguata
   b) Correzione della coagulopatia (AT-III, plasma, Vit. K)
   c) Analgesia adeguata
   d) Somministrazione di O2 e/o supporto ventilatorio qualora necessario
   e) Paracentesi in caso di impegno respiratorio non controllabile con la terapia diuretica
   f) Terapia delle infezioni spesso associate

2. Terapia contro la patologia microtrombotica

- Fibrinolisi tramite tissue-plasminogen activator (t-PA)

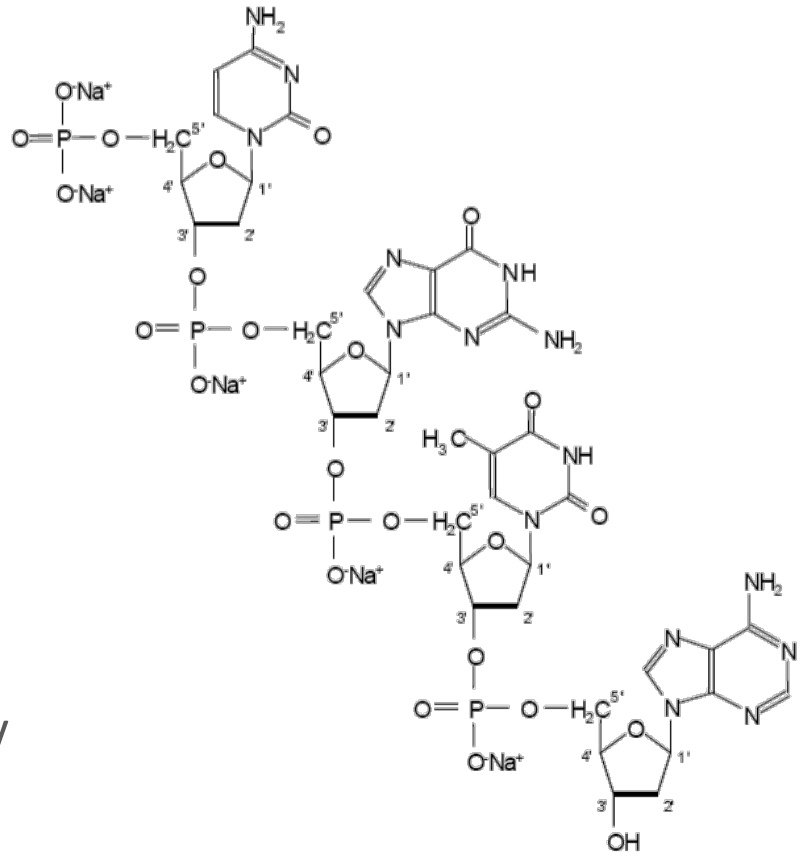
→ complicanze emorragiche severe

3. Metilprednisolone può essere preso in considerazione

Defibrotide: a promising drug for the treatment of VOD

Defibrotide is:

- A mixture of oligonucleotides obtained from porcine intestinal mucosa
- Prepared by controlled depolymerisation of DNA
- Available in vials containing 200 mg solution for IV administration



4. DEFIBROTIDE

- Oligonucleotide con un peso molecolare di 23 kDa che esercita il suo effetto come agonista del recettore dell'adenosina

-Proprietà antischemiche, antitrombotiche e antinfiammatorie:

-**Effetto antitrombotico**: aumenta l'attività fibrinolitica plasmatica, ma: basso rischio di complicanze emorragiche (effetto prevalentemente locale)

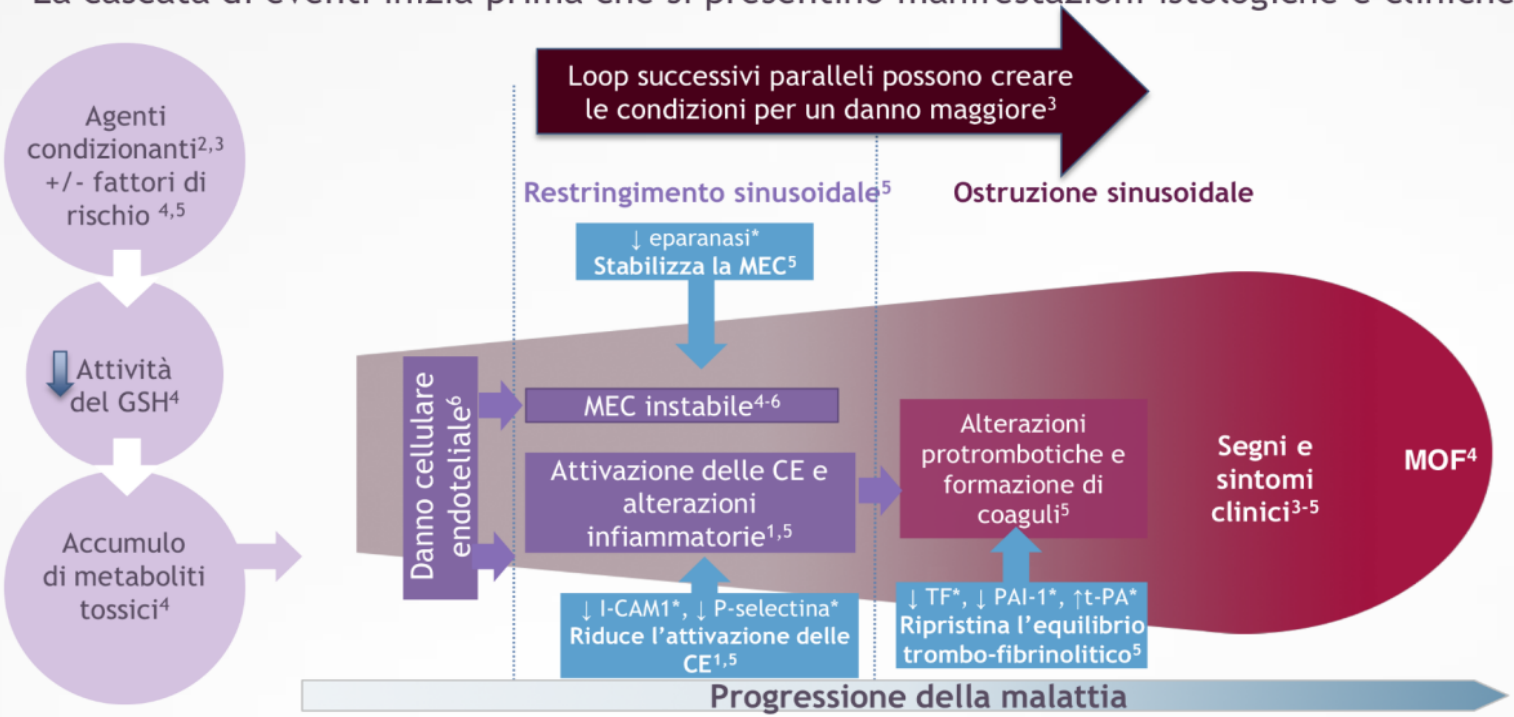
-**Effetto antischemico**: promuove la proliferazione endoteliale con una maggiore rivascolarizzazione dopo un danno a livello endoteliale

-**Effetto antinfiammatorio**: come agonista del recettore dell'adenosina, riduce l'espressione di molecole di adesione e previene in questo modo la comparsa di mediatori infiammatori

Indicato nella terapia della VOD

Il danno e l'attivazione delle cellule endoteliali determinano una cascata progressiva di eventi [1]

La cascata di eventi inizia prima che si presentino manifestazioni istologiche e cliniche[2,3]



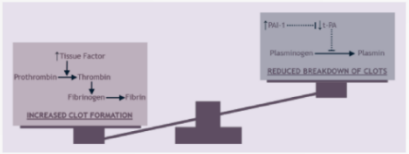
Adattato da Pescador *et al* 2013, DeLeve 2011, Richardson *et al* 2013, Carreras 2011; Carreras 2012[1-5]

Defitelio esercita effetti mediati dalla cellula endoteliale nell'ambito delle maggiori cascate di eventi della sVOD[2,4]

GSH, enzima glutatione; MEC, matrice extracellulare; CE cellula endotelialel; ICAM-1, molecola di adesione intercellulare 1; P-selectina, selectina piastrinica; TF, fattore tissutale; PAI-1, inibitore dell'attivatore del plasminogeno; t-Pa, attivatore tissutale del plasminogeno; TCSE, terapia con trapianto di cellule staminali ematopoietiche; MOF, insufficienza multiorgano

1. Pescador R, et al. Vascular Pharmacology 2013; 59(1): 1–10. 2. DeLeve LD, et al. Vascular Liver Disease and the Liver Sinusoidal Endothelial Cell. Vascular Liver Disease: Mechanisms and Management. New York: Springer, 2011: 25–40. 3. Carreras E and Diaz-Ricart M. Bone Marrow Transplant 2011; 46: 4. Carreras E. Chapter 11: Early complications after HSCT. EBMT-ESH Handbook 2012: 176–195. 5. Richardson PG, et al. Biol Blood Marrow Transplant 2013; 19: S88–90. 6. Defitelio® Summary of Product Characteristics March 2015

[redacted] ripristina l'equilibrio trombo-fibrinolitico[1-2]



In vitro

[redacted] ↓Fattore tissutale

Riduzione dell'attività procoagulante[1]

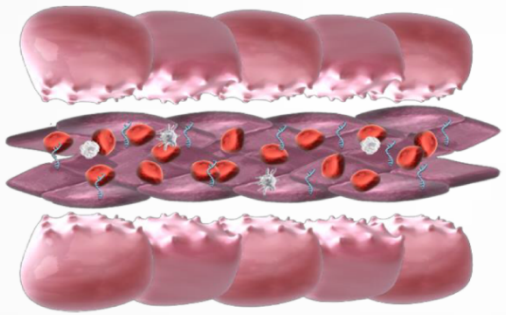
RIDOTTA FORMAZIONE DI COAGULI

In vitro

[redacted] ↓PAI-1 ↑t-PA

Aumento del potenziale fibrinolitico

MAGGIORE DEGRADAZIONE DEI COAGULI



> Defitelio® ripristina l'equilibrio trombo-fibrinolitico [1,2] mediante un doppio approccio mediato dalla cellula endoteliale sulla cascata della coagulazione[2]

1. Defitelio® Summary of Product Characteristics March 2015. 2. Falanga A. Leukemia. 2003; 17: 1636–1642.

PAI-1, inibitore dell'attivatore del plasminogeno-1; T-Pa, attivatore tissutale del plasminogeno

[redacted] ha come bersaglio la cellula endoteliale e svolge azioni multifattoriali per trattare la sVOD[1]

> [redacted] esercita effetti mediati dalla cellula endoteliale sulle maggiori cascate di eventi nella sVOD[2-4]

	Restringimento sinusoidale		Ostruzione sinusoidale
Fisiopatologia VOD	MEC instabile e alterazioni strutturali[3]	Attivazione delle CE Alterazioni infiammatorie[1,6,7]	Formazione di coaguli e alterazioni protrombotiche[3]
	↑Eparanasi[3]	↑ Molecole di adesione (ICAM-1[2], selectine)[3,8]	↑ Fattore tissutale ↑ PAI-1[2], ↓t-PA[3]
MOA di Defitelio®	↓Espressione, attività dell'eparanasi[2,5]	↓ Molecole di adesione (ICAM-1, P-selectina)[3,9,10]	↓ Espressione TF ↓ PAI-1[2], ↑t-PA[11]
	Contribuisce all'integrità della MEC[2]	Riduce l'attivazione delle CE[2,8]	Ripristina l'equilibrio trombo-fibrinolitico[2]

MEC, matrice extracellulare; CE, cellula endoteliale; ICAM-1, molecola di adesione intercellulare 1; P-selectina, selectina piastrinica; PAI-1, inibitore dell'attivatore del plasminogeno-1; t-Pa, attivatore tissutale del plasminogeno; TF, fattore tissutale; MOA, meccanismo d'azione (mode of action)

1. Pescador R, et al. Cardiovasc Drug Rev 2000; 18(4): 304–311. 2. Defitelio® Summary of Product Characteristics March 2015. 3. Richardson PG, et al. Biol Blood Marrow Transplant 2013; 19: S88–90. 4. DeLeve LD, et al. Vascular Liver Disease and the Liver Sinusoidal Endothelial Cell. Vascular Liver Disease: Mechanisms and Management. New York: Springer, 2011: 25–40. 5. Mitsiades CS, et al. Clin Cancer Res 2009; 15: 1210–1221. 6. Carreras E and Diaz-Ricart M. Bone Marrow Transplant 2011; 46: 1495–1502. 7. Félétou M. Chapter 2: Multiple Functions of the Endothelial Cells. The Endothelium —Focus on Endothelium-Derived Vasoactive Mediators. San Rafael (CA): Morgan & Claypool Life Sciences, 2011. 8. Pescador R, et al. Vascular Pharmacology 2013; 59(1): 1–10. 9. Palomo M, et al. Biol Blood Marrow Transplant 2011; 17: 497–506. 10. Scalia R, et al. Meth Find Exp Clin Pharmacol 1996; 18: 669–676. 11. Falanga A. Leukemia. 2003; 17: 1636–1642.

La terapia con [redacted] è supportata da evidenze cliniche chiare e concordanti[1-3]

[redacted]

> [redacted] riassunto dei principali risultati di efficacia in studi clinici[1]

Outcome	*Sperimentazione pilota (25 mg/kg/die)*[1] *(luglio 2006 - novembre 2008)*		*Programma internazionale di uso compassionevole (pazienti sVOD)*[1] *(dicembre 1998 - marzo 2009)*	*Studio in aperto T-IND (25 mg/kg/die)*[1] *(dicembre 2007 - in corso)*	*Dati da un registro US*[1] *(ottobre 2008 - dicembre 2011)*[¥]		*Studio di determinazione della dose (25 mg/kg/die)*[1] *(aprile 2000 - maggio 2007)*
	Controllo storico[1]	Defitelio®[1]			Non trattato con Defitelio®[1]	Trattato con Defitelio®[1]	
Risposta completa al giorno +100	9,4%	23,5%	24,1%	25,9%	29,0%	51,0%	43,0%
	p=0,0131						
Soprav-vivenza al giorno +100	25,0%*	38,2%*	36,8%	44,8%*	31,0%	39,0%	43,9%*
	p=0,0341						

Adattato da Defitelio® Riassunto delle caratteristiche del prodotto , Marzo 2015 [1] & Defitelio® EMA Assessment Report October 2013 [2]
*Stime di Kaplan-Meier per l'analisi tempo all'evento fino al giorno +100 post TCSE
¥ = Specifiche informazioni sulla dose non sono state raccolte

EMA, agenzia europea per i medicinali,

1. Defitelio® Summary of Product Characteristics March 2015. 2. Defitelio® European Public Assessment Report. EMA procedure No./H/C/002393. July 2013. 3. Recommendation for maintenance of orphan designation at the time of marketing authorisation. Defitelio® (defibrotide) for the treatment of hepatic veno-occlusive disease. November 2013.

Biol Blood Marrow Transplant 22 (2016) 400–409

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Review Articles

Hepatic Veno-Occlusive Disease after Hematopoietic Stem Cell Transplantation: Risk Factors and Stratification, Prophylaxis, and Treatment

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Article history:
Received 15 July 2015
Accepted 24 September 2015

Key Words:
Hepatic veno-occlusive disease
Prophylaxis
Risk factors
Sinusoidal obstruction syndrome
Stem cell transplantation
Treatment

A B S T R A C T

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), can develop in a subset of patients, primarily after myeloablative hematopoietic stem cell transplantation, but it also may occur after reduced-intensity conditioning. Severe VOD/SOS, typically characterized by multiorgan failure, has been associated with a mortality rate greater than 80%. Therefore, an accurate and prompt diagnosis of VOD/SOS is essential for early initiation of appropriate therapy to improve clinical outcomes. Moreover, some studies have support the use of prophylaxis for patients who are at high risk of developing VOD/SOS. This review summarizes risk factors associated with development of VOD/SOS, including pretransplantation patient characteristics and factors related to stem cell transplantation, that can facilitate patient stratification according to risk. The incidence of VOD/SOS, clinical features, and diagnostic criteria are reviewed. Data on emerging treatment strategies for patients with VOD/SOS are discussed in the context of recent treatment guidelines. Additionally, options for prophylaxis in individuals who are at increased risk are presented. Although historically only those patients with moderate to severe VOD/SOS have been treated, early therapy and prophylaxis may be appropriate for many patients and may have the potential to improve patients' outcomes and survival, including for those with nonsevere disease.

INTRODUCTION

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a well-recognized and potentially life-threatening complication that occurs primarily after myeloablative hematopoietic stem cell transplantation (HSCT), but it also has been observed in patients after reduced-intensity conditioning (RIC) and rarely after exposure to hepatotoxic chemotherapies outside the transplantation framework [1]. VOD/SOS was initially described in patients who had ingested bush tea containing pyrrolizidine alkaloids. Although associated with multiple clinical settings, such as hepatic irradiation and use of azathioprine, or more recently gemtuzumab ozogamicin, VOD/SOS is most commonly seen in the context of high-dose chemotherapy with HSCT, where it was first described in 1979 [2]. Initial case series reported fatality rates of 50% or higher [3]. VOD/SOS has been reported as a leading cause of death in the post-transplantation period, with interstitial pneumonia, infections, and graft-versus-host disease (GVHD) as the other leading causes [4]. Patients with moderate or severe VOD/SOS (sVOD/sSOS; typically characterized by multiorgan failure [MOF]) with ascites and hypertension, can have significant morbidity and mortality. sVOD/sSOS is associated with a mortality rate higher than 80% [1].

During the past 10 years, our understanding of the risk factors for developing VOD/SOS has improved, and new therapeutic strategies have emerged that allow for better prevention and treatment of this devastating complication. Herein, we provide a review of the current understanding of VOD/SOS, its prevention, and treatment.

PATHOPHYSIOLOGY OF VOD/SOS

VOD/SOS arises from endothelial cell damage and hepatocellular injury due to the transplantation conditioning regimen. Although its pathophysiology is not completely understood, the complex pathogenesis begins with injury

Financial disclosure: See Acknowledgments on page 407.

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http://dx.doi.org/10.1016/j.bbmt.2015.09.024
1083-8791/

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure

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Key Points

- Defibrotide improves day +100 survival and CR in patients with VOD and MOF compared with a historical control.
- The historical control selection methodology offers a novel approach for investigation of a life-threatening orphan disease.

Hepatic veno-occlusive disease (VOD), also called sinusoidal obstruction syndrome (SOS), is a potentially life-threatening complication of hematopoietic stem cell transplantation (HSCT). Untreated hepatic VOD/SOS with multi-organ failure (MOF) is associated with >80% mortality. Defibrotide has shown promising efficacy treating hepatic VOD/SOS with MOF in phase 2 studies. This phase 3 study investigated safety and efficacy of defibrotide in patients with established hepatic VOD/SOS and advanced MOF. Patients (n = 102) given defibrotide 25 mg/kg per day were compared with 32 historical controls identified out of 6867 medical charts of HSCT patients by blinded independent reviewers. Baseline characteristics between groups were well balanced. The primary endpoint was survival at day +100 post-HSCT; observed rates equaled 38.2% in the defibrotide group and 25% in the controls (23% estimated difference; 95.1% confidence interval [CI], 5.2-40.8; *P* = .0109, using a propensity-adjusted analysis). Observed day +100 complete response (CR) rates equaled 25.5% for defibrotide and 12.5% for controls (19% difference using similar methodology; 95.1% CI, 3.5-34.6; *P* = .0160). Defibrotide was generally well tolerated with manageable toxicity. Related adverse events (AEs) included hemorrhage or hypotension; incidence of common hemorrhagic AEs (including pulmonary alveolar [11.8% and 15.6%] and gastrointestinal bleeding [7.8% and 9.4%]) was similar between the defibrotide and control groups, respectively. Defibrotide was associated with significant improvement in day +100 survival and CR rate. The historical-control methodology offers a novel, meaningful approach for phase 3 evaluation of orphan diseases associated with high mortality. This trial was registered at www.clinicaltrials.gov as #NCT00358501. (*Blood*. 2016;00(00):1-10)

Submitted October 21, 2015; accepted January 22, 2016. Prepublished online as *Blood* First Edition paper, January 29, 2016; DOI 10.1182/blood-2015-10-676924.

The online version of this article contains a data supplement.

There is an Inside *Blood* Commentary on this article in this issue.

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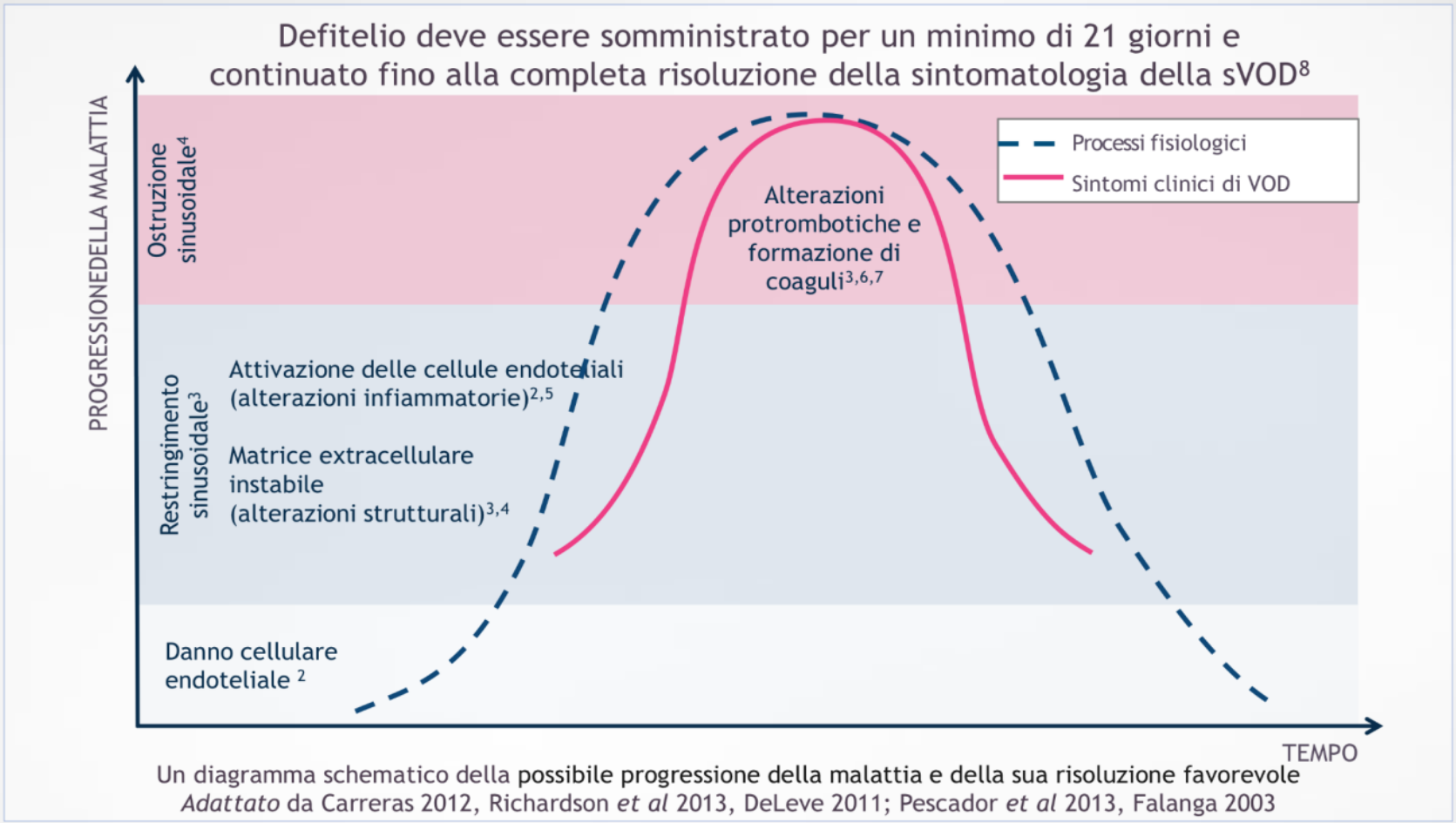
La progressione della malattia è imprevedibile[1]



Un diagramma schematico della possibile progressione della malattia e della sua risoluzione favorevole
Adattato da Carreras 2012, Richardson *et al* 2013, DeLeve 2011; Pescador *et al* 2013, Falanga 2003

VOD, malattia veno-occlusiva

1. Schoppmeyer K, et al. Z Gastroenterol 2006; 44(6): 483–486. 2. Carreras E. Chapter 11: Early complications after HSCT. EBMT-ESH Handbook 2012: 176–195. 3. Richardson PG, et al. Biol Blood Marrow Transplant 2013; 19: S88–90. 4. DeLeve LD, et al. Vascular Liver Disease and the Liver Sinusoidal Endothelial Cell. Vascular Liver Disease: Mechanisms and Management. New York: Springer, 2011: 25–40. 5. Pescador R, et al. Cardiovasc Drug Rev 2000; 18(4): 304–311. 6. Baron F, et al. Haematologica 1997; 82: 718–725. 7. Falanga A. Leukemia. 2003; 17: 1636–1642. 8. Defitelio® Summary of Product Characteristics March 2015.

European paediatric prevention (EPP) study

Eudra-CT 2004-000592-33

Conclusions

- Defibrotide significantly reduced:
  - The incidence of VOD by 40%
  - The risk of VOD-related morbidity (MOF, in particular renal failure) and mortality
  - The risk and severity of acute GvHD
  - The need for corticosteroids

- Defibrotide was generally well tolerated
  - Resulting in few drug-related AEs (5%) and drug-related SAEs (1%)

Defibrotide reduces the incidence of VOD in high-risk paediatric patients undergoing SCT

Corbacioglu S. Pediatric trial investigating the incidence and outcome of veno-occlusive disease with the prophylactic use of defibrotide (VOD-Defibrotide), NCT00272948, data on file, http://clinicaltrials.gov/ct2/show/NCT00272948?term=defibrotide&rank=2

Delayed treatment reduces survival

Survival by Day 100 post-SCT		
Delay ≤2 days	Delay >2 days	p value
45%	22%	0.0237

- Subjects that started defibrotide therapy within 2 days from the date of VOD diagnosis, had a significantly improved mortality rate at Day 100 post-SCT

Richardson PG. Defibrotide for patients with hepatic veno-occlusive disease (VOD): a treatment IND study, NCT00628498, data on file, http://clinicaltrials.gov/ct2/show/NCT00628498?term=defibrotide&rank=5

Studio clinico interventistico che non prevede l'utilizzo di medicinale
Codice del protocollo: ELASTOVOD

Studio prospettico monocentrico per valutare il potenziale diagnostico dell'elastometria epatica e di scores biochimici e strumentali di predire lo sviluppo di complicanze severe del fegato in pazienti sottoposti a trapianto di cellule staminali emopoietiche (TCSE)

PI: Dott. Antonio Colecchia
Dipartimento dell'Apparato Digerente, U.O. Gastroenterologia

Obiettivo primario

Individuare dei valori rilevati con TE e scores biochimici pre-trapianto e/o un loro incremento come fattore indipendente di aumentato rischio di sviluppare una epatopatia trapianto-correlata.

Popolazione dello studio

CRITERI DI INCLUSIONE
- età compresa tra 4-70 anni
- maschi e femmine
- pazienti affetti da malattia onco-ematologica con indicazione al trapianto allogenico ed autologo di CSE; tra i pazienti con indicazione al trapianto autologo vengono inclusi quelli che sono stati sottoposti a TBI o a chemioterapia ablativa basata sull'uso di Busulfano
- ottenimento consenso informato

CRITERI DI ESCLUSIONE
- obesità patologica (BMI>40)
- pacemaker o defibrillatori impiantabili
- presenza di versamento ascitico

Disegno dello studio

All'arruolamento (T0, prima dell'inizio della chemioterapia pre-TCSE),
tutti i pazienti sono sottoposti a:
- valutazione clinica e laboratoristica*
- ecografia dell'addome completo
- elastometria epatica (TE)

Successivamente, la TE e valutazione clinico-laboratoristica viene ripetuta a 7-10 (T1), 17-20 (T2) e a 27-30 (T3) giorni dal trapianto.
In presenza di valori ematici suggestivi di danno epatico, viene eseguita un'ecografia dell'addome superiore e successivamente la TE ogni 5 giorni per un totale di 4 misurazioni.

**Emocromo completo con formula, AST, ALT, Bilirubina totale e frazionata, Albumina sierica, Creatinina sierica, INR, PT, aPTT, fibrinogeno, GGT, Fosfatasi alcalina, colinesterasi, PCR, Ciclosporina sierica, FK sierico*

Dati preliminari
(Raccolta dati novembre 2014 – gennaio 2016)

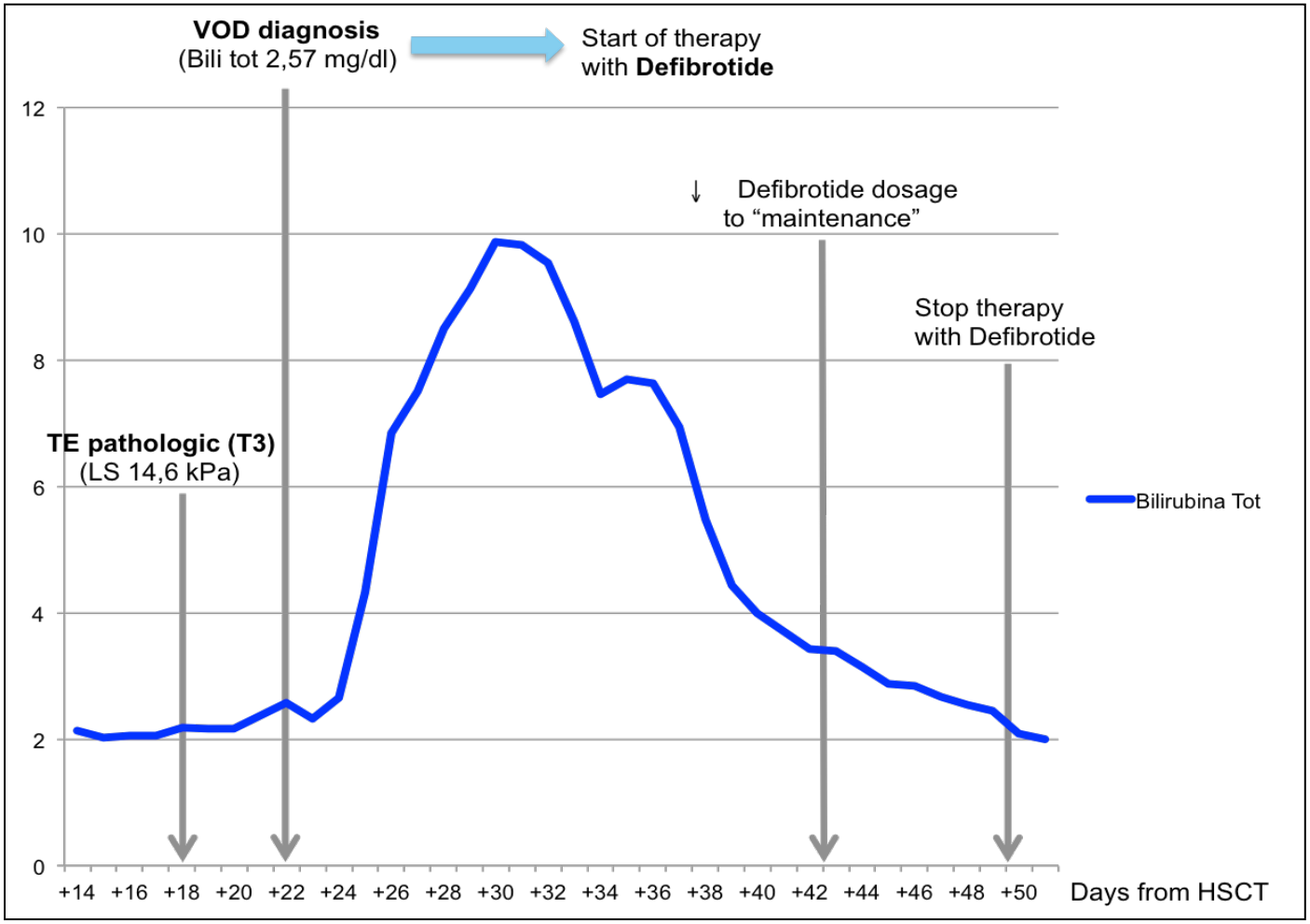
	Frequency	(%)
Age		
< 6.7 y	4	(30.8)
> 6.7 y	9	(69.2)
Sex		
M	10	(77.0)
F	3	(23.0)
Diagnosis		
ALL	4	(30.8)
AML	4	(30.8)
Ewing Sarcoma	1	(7.7)
Severe aplastic anemia	2	(15.4)
Beta-thalassemia	2	(15.4)
Type of SCT		
Allogenic	12	(92.3)
MUD	3	(25.0)
PMUD	4	(33.3)
MFD	4	(33.3)
PMFD	1	(8.4)
Autologous	1	(7.7)
Conditioning regimen		
BU-MEL	1	(7.7)
BU-MEL-CPM-ATG	1	(7.7)
BU-THIO-CPM + ATG	3	(23.0)
BU-THIO-FLUDA-ATG	1	(7.7)
TREO-FLUDA-MEL-ATG	1	(7.7)
TREO-FLUDA-THIO + ATG	4	(30.8)
TREO-FLUDA-THIO-CPM_{post}	1	(7.7)
FLUDA-CPM-ATG	1	(7.7)
Severe hepatotoxicity		
Yes	6	(46.2)
Diagnosis von VOD	3	(23.0)
No	7	(53.8)

M=male, F=female,
BU=busulphan, MEL=melphalan,
CPM=cyclophosphamide,
CPM_{post}= CPM after HSCT,
ATG= anti thymocyte globulin,
THIO=thiotepa, TREO=treosulfan,
FLUDA= fludarabine

Liver Stiffness (LS) measurement (kPa)

	LS-T0	LS_T1	LS_T2	LS_T3
Pat 1	5,9	6,1	4,5	4,8
Pat 2	5,0	4,1	4,3	14,6
Pat 3	5,0	3,5	3,3	4,0
Pat 4	3,5	4,5	10,3	--
Pat 5	6,1	5,9	7,7	49,6
Pat 6	4,8	4,0	4,7	14,9
Pat 7	4,1	4,4	5,1	4,7
Pat 8	4,6	8,2	10,4	17,3
Pat 9	4,9	5,5	6,1	5,1
Pat 10	4,4	4,1	3,3	5,0
Pat 11	4,8	5,4	3,9	4,4
Pat 12	3,9	3,2	3,5	3,7
Pat 13	7,7	3,4	6,8	3,4
p50	4,8	4,4	4,7	4,9
mean	5,0	4,79	5,68	10,96
sd	1,1	1,39	2,46	13,18

M.K. (f), 12 aa, LAL rec, donatore MUD (HLA full match),
regime di condizionamento: busulfano, thiotepa, ciclofosfamide



Not always change equates to improve,
but to improve must change