TAVOLA ROTONDA
COMPLICAZIONI TRAPIANTOLOGICHE: LA VOD NEL TCSE

Casi Clinici

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TMO
AOU Careggi - Firenze

UPN 1771

- D.O.B. 8/6/1995 0+ kg 64
- 10-2015 LAL B cariotipo complesso no riarrangiamenti 11q23
- NILG ALL 10/07 per 4 cicli RC mrd negativa
- Rescue CSE autologhe con Hyper-CVAD B
- Figlio unico, no MUD ma un CB 6/8
- Fugace positivizzazione mrd ma va al trapianto mrd negativo
- TBF MAC ATG 6 mg/kg CSA MMF (studio gandalf)
- CBT 5/6 ma 6/8 F A+ 11-4-2016 2 TNC x 10^7/Kg CD34+ 0,8 x 10^6Kg
- Attecchimento completo granulocitario e chimerismo completo
- Complicazioni:
  - In degenza : sepsi da KP multisensibile, esofagite HSV, TA-TMA trattata con stop CSA PFC eculizumab HHV 6 Foscarnet + IG
  - Cistite emorragica trattata con gel piastrinico, micosi seno mascellare destro B glucano pos : isovuconazolo.
  - 4 ricoveri per CMV refrattario a val/ganciclovir foscarnet e cidofovir . Mutazione UL97 A594V resistente a val/ganciclovir UL54 A834P a ganciclovir foscarnet e cidofovir UL54 A809Va ganciclovir e foscarnet risolti alla tardiva ricostituzione immunologica CD 4 > 200 a 10 mesi
  - VZV trigeminale a Dicembre 2017
- Recidiva mieloide FLT3+ 47 XX+6 il 4-12-2017 cutanea e BM su cellule del CB
- Trattato con IDA ARA-C poi MEC + HD-ARA-C con refrattarietà -> Aplo

Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT)

M Mohty[1,32], F Malard[1,32], M Abecassis[2,32], E Aerts[3,32], AS Alaskar[4,32], M Aljurf[5,32], M Arat[6,32], P Bader[7,32], F Baron[8,32], A Bazarbachi[9,32], D Blaise[10,32], F Ciceri[11,32], S Corbacioglu[12,32], J-H Dalle[13,32], RF Duarte[14,32], T Fukuda[15,32], A Huynh[16,32], T Masszi[17,32], M Michallet[18,32], A Nagler[19,32], M NiChonghaile[20,32], T Pagluica[21,32], C Peters[22,32], FB Petersen[23,32], PG Richardson[24,32], T Ruutu[25,32], BN Savani[26,32], E Wallhult[27,32], I Yakoub-Agha[28,32] and E Carreras[29,30,31,32]

Table 1. Traditional risk factors for SOS/VOD

Risk factors

Transplant-related
- Allo-HSCT > auto-HSCT
- Unrelated donor
- HLA-mismatched donor
- Myeloablative conditioning regimen
- BU-based conditioning regimen
- TBI-based conditioning regimen
- Non-T-cell-depleted graft
- Second HSCT

Patient- and disease-related
- Older > younger (in adult patients)
- Female receiving norethisterone
- Karnofsky score below 90%
- Gene polymorphism (GSTM1, GSMTT1, heparanase)
- Advanced disease (beyond second CR or relapse)
- Metabolic syndrome
- Deficit of AT III, t-PA and resistance to activated protein C
- Thalassemia

Hepatic related risk factors
- Transaminase > 2.5 ULN
- Serum bilirubin > 1.5 ULN
- Cirrhosis
- Hepatic fibrosis
- Active viral hepatitis
- Hepatic irradiation
- Previous use of gemtuzumab ozogamicin
- Use of hepatotoxic drugs
- Iron overload

Pediatric specific risk factors
- Hemophagocytic lymphohistiocytosis, adrenoleucodystrophy, osteopetrosis
- High-dose auto-HSCT in neuroblastoma
- Young age (under 1–2 years of age)
- Low weight
- Juvenile myelo-monocytic chronic leukemia

Abbreviations: AT III = antithrombin III; HSCT = hematopoietic SCT; SOS/VOD = sinusoidal obstruction syndrome or veno-occlusive disease; t-PA = tissue plasminogen activator; ULN = upper limit of normal.

Bone Marrow Transplantation (2015) **50,** 781–789

UPN 1771

Marca con X	Fattori di rischio associati al **TRAPIANTO**
	Donatore non familiare
V	Donatore non HLA identico
V	Trapianto non T-depleto
V	Regime di Condizionamento Mieloablativo
V	Busulfano Orale o Busulfano ad Alto Dosaggio
	TBI ad Alte Dosi
V	Secondo Trapianto
	Altro:
	Altro:

Marca con X	Fattori di rischio associati al **FEGATO**
	Transaminasi > 2,5 ULN
	Bilirubina Sierica > 1,5 ULN
	Cirrosi Epatica
	Epatite Virale Attiva
	Irradiazione Addominale o Epatica
	Precedente Trattamento con Gemtuzumab Ozogamicina
	Precedente Trattamento con Inotuzumab Ozogamicina
	Utilizzo di Farmaci Epatotossici
V	Sovraccarico di Ferro
	Altro:
	Altro:

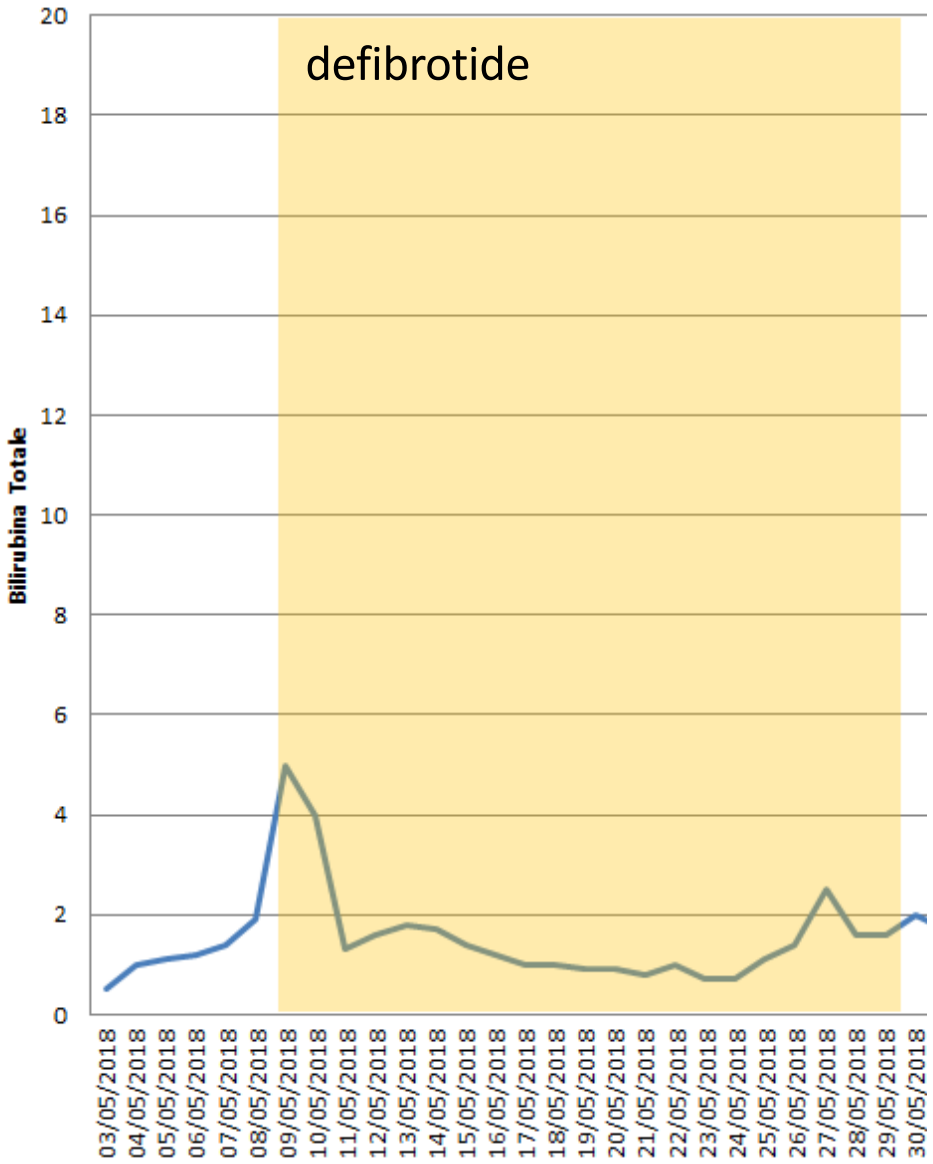
Marca con X	Fattori di rischio associati al **PAZIENTE**
	Età Avanzata
	Sindrome Metabolica
	Donna in Trattamento con Noretisterone
V	Malattia Avanzata (oltre la seconda CR o ricaduta/refrattarietà)
	Diagnosi di Talassemia
	Fattori Genetici (Polimorfismo GSTM1; Allele C282Y; Aplotipo MTHFR 677cc/1298CC)
	PEDIATRICO: Età di Insorgenza della Malattia Primaria (Maggiore Rischio in Età Minore)
	PEDIATRICO: Osteopetrosi Infantile
	PEDIATRICO: Sindromi Congenite da Attivazione Macrofagica, come Linfoistiocitosi Emofagocitica Familiare (HLH), Sindrome di Griscelli e Malattia Linfoproliferativa X-correlata
	PEDIATRICO: Talassemia con Epatomegalia ed Elevato Sovraccarico di Ferro
	PEDIATRICO: Neuroblastoma ad Alto Rischio
	PEDIATRICO: Anemia a Cellule Falciformi*
	Altro:
	Altro:

* Potenziali rischi associati

Note

UPN 1771 II

- II TMO Aplo dal padre (1961) M kg 84 0+ CMV ed EBV + no trasfusioni
- Paziente M 47 kg A+ CMV + EBV + Toxo + Sorror 3 per DLCO 65% in recidiva refrattaria e blastosi perferica e midollare
- PBSCT 11,8 x 10^6 CD34+/kg il 24-4-2018 TBF MAC + CSA +MMF + CY post
- Attecchimento leucocitario in + 18 (12/5/18)
- 9/5/18 ittero (bilirubina 5), ascite, aumento di peso, dolore ipocondrio,
- Biopsia transgiugulare con misurazione delle pressioni (HVPG 15) che risultano come l' istologia coerenti con VOD SOS . Inizia defibrotide (9-5-18) steroide e diuretici con pieno recupero di ittero ed ascite e sospensione del defibrotide (29-5-18) a tre settimane di terapia.
- Riattivazione CMV 22-5-2018 responsivo a terapia preemptive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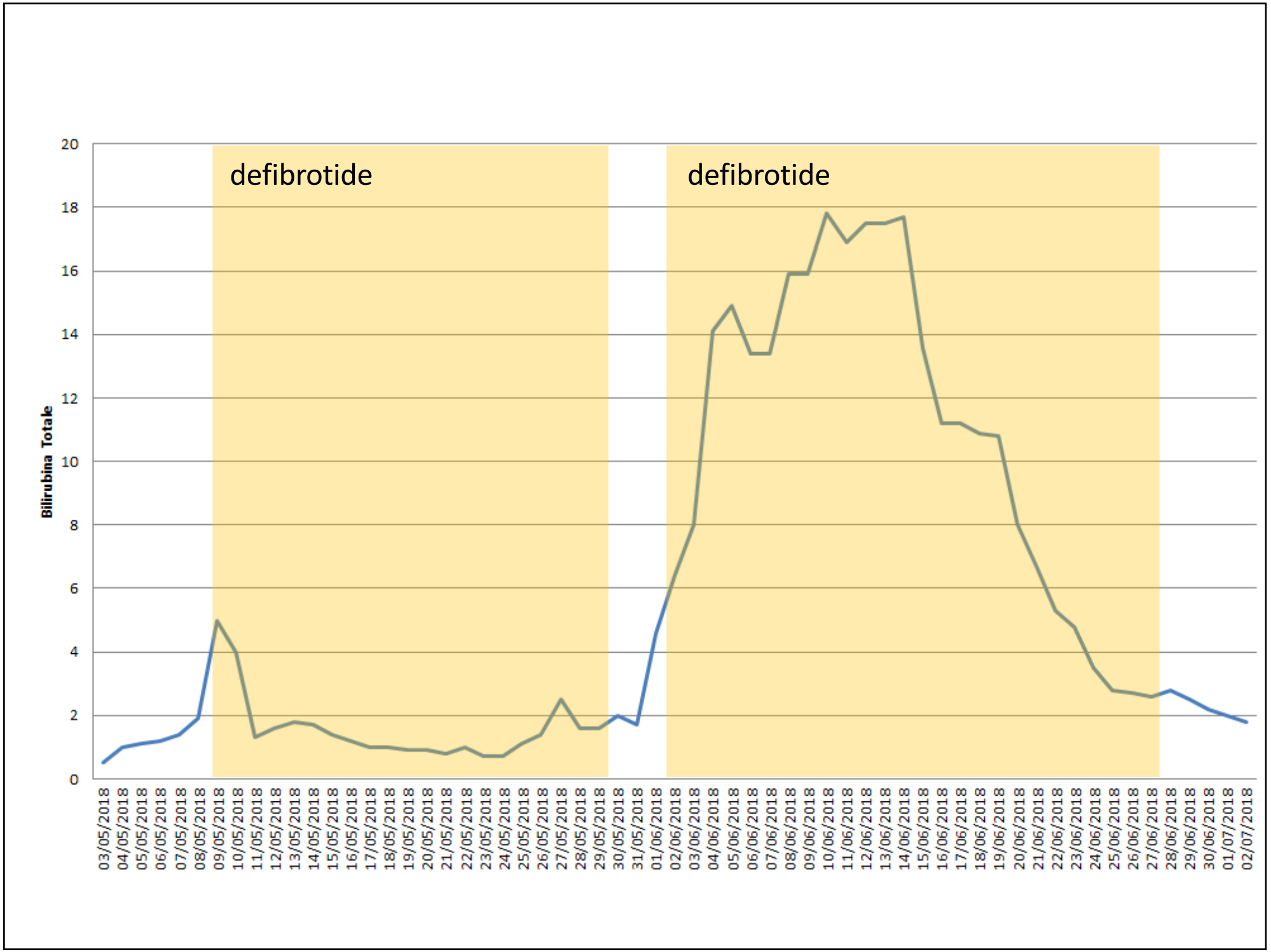
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02/07/2018

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- Riattivazione CMV 22-5-2018 responsivo a terapia preemptive
- Nuovo episodio dal 2-6-18 con ittero (bilirubina 18) e ascite ritrattato con Defibrotide dal 2-6-18 al 26-6-18 con risposta completa e duratura
- TA TMA in Eculizumab 900 mg settimanale dall' 8/6 per anemia microangiopatica con schistocitosi (20)
- Recidiva 13-8-18
- Decesso 18-8-18

UPN 1771 II primo episodio

Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation

M Mohty[1,32], F Malard[1,32], M Abecassis[2,32], E Aerts[3,32], AS Alaskar[4,32], M Aljurf[5,32], M Arat[6,32], P Bader[7,32], F Baron[8,32], A Bazarbachi[9,32], D Blaise[10,32], F Ciceri[11,32], S Corbacioglu[12,32], J-H Dalle[13,32], F Dignan[14,32], T Fukuda[15,32], A Huynh[16,32], T Masszi[17,32], M Michallet[18,32], A Nagler[19,32], M NiChonghaile[20,32], S Okamoto[21,32], A Pagliuca[22,32], C Peters[23,32], FB Petersen[24,32], PG Richardson[25,32], T Ruutu[26,32], BN Savani[27,32], E Wallhult[28,32], I Yakoub-Agha[29,32], RF Duarte[30,32] and E Carreras[31,32]

Table 3. New EBMT criteria for severity grading of a suspected SOS/VOD in adults

	Mild[a]	*Moderate*[a]	*Severe*	*Very severe - MOD/MOF*[b]
Time since first clinical symptoms of SOS/VOD[c]	>7 Days	5–7 Days	V ⩽4 Days	Any time
Bilirubin (mg/dL) Bilirubin (μmol/L)	⩾2 and <3 ⩾34 and <51	V ⩾3 and <5 ⩾51 and <85	⩾5 and <8 ⩾85 and <136	⩾8 ⩾136
Bilirubin kinetics			Doubling within 48 h	
Transaminases	⩽2 × normal	> 2 and ⩽5 × normal	>5 and ⩽8 × normal	>8×Normal
Weight increase	< 5%	⩾5% and <10%	⩾5% and <10%	V ⩾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

Abbreviations: EBMT = European society for Blood and Marrow Transplantation; MOD = multi-organ dysfunction; MOF = multi-organ failure; SOS = sinusoidal obstruction syndrome; VOD = veno-occlusive disease. Patients belong to the category that fulfills two or more criteria. If patients fulfill two or more criteria in two 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. [a]In the case of presence of two or more risk factors for SOS/VOD, patients should be in the upper grade. [b]Patients with multi-organ dysfunction must be classified as very severe. [c]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.

Bone Marrow Transplantation (2016) **51,** 906–912

UPN 1771 II secondo episodio

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Bilirubin (mg/dL) Bilirubin (μmol/L)	⩾2 and <3 ⩾34 and <51	⩾3 and <5 ⩾51 and <85	⩾5 and <8 ⩾85 and <136	V ⩾8 ⩾136
Bilirubin kinetics			Doubling within 48 h	V
Transaminases	⩽2 × normal	>2 and ⩽5 × normal	>5 and ⩽8 × normal	>8 × Normal
Weight increase	<5%	⩾5% and <10%	⩾5% and <10%	V ⩾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

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Table 2. New EBMT criteria for SOS/VOD diagnosis in adults

Classical SOS/VOD In the first 21 days after HSCT	*Late onset SOS/VOD* >21 Days after HSCT
Bilirubin ⩾2 mg/dL and two of the following criteria must be present:	Classical VOD/SOS beyond day 21
	OR
Painful hepatomegaly	Histologically proven SOS/VOD
Weight gain >5%	OR
Ascites	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

Abbreviations: EBMT = European Society for Blood and Marrow Transplantation; SOS = sinusoidal obstruction syndrome; VOD = veno-occlusive disease. These symptoms/signs should not be attributable to other causes.

UPN 1738

- D.O.B. 1/10/1969 0+ kg 65
- 5-2015 LAM cariotipo normale FLT3 e NPM1 wild type
- ICE → RD
- A 20 → RC morfologica mrd neg consolidato con 2 HD ARA-C
- Un fratello aploidentico, madre pregresso LH
- Ferritina 1798
- TBF MAC ATG 5 mg/kg CSA MTX
- MUD 7/8 ma 9/10 (mm B37 vs 44 DPB non permissivo) M A+ 25-11-2015 CD34+ 8,37 x 10^6Kg
- Attecchimento completo granulocitario +14 e piastrinico +12 e chimerismo completo
- Complicazioni:
  - In degenza : Mucosite severa, FUO, e a +19 aGvHD cute ++-- grading complessivo +
  - 24/12 e 15/2 riattivazione CMV trattate con Valganciclovir
- 24-2-16 ricovero in Medicina Generale per melena con piastrinopenia e gastrite emorragica, concomitanti riattivazione CMV (ganciclovir e foscarnet)

UPN 1738

Marca con X	Fattori di rischio associati al **TRAPIANTO**	
V	Donatore non familiare	
V	Donatore non HLA identico	
V	Trapianto non T-depleto	
V	Regime di Condizionamento Mieloablativo	
V	Busulfano Orale o Busulfano ad Alto Dosaggio	
	TBI ad Alte Dosi	
	Secondo Trapianto	
	Altro:	
	Altro:	

Marca con X	Fattori di rischio associati al **FEGATO**	
	Transaminasi > 2,5 ULN	
	Bilirubina Sierica > 1,5 ULN	
	Cirrosi Epatica	
	Epatite Virale Attiva	
	Irradiazione Addominale o Epatica	
	Precedente Trattamento con Gemtuzumab Ozogamicina	
	Precedente Trattamento con Inotuzumab Ozogamicina	
	Utilizzo di Farmaci Epatotossici	
V	Sovraccarico di Ferro	
	Altro:	
	Altro:	

Marca con X	Fattori di rischio associati al **PAZIENTE**	
	Età Avanzata	
	Sindrome Metabolica	
	Donna in Trattamento con Noretisterone	
	Malattia Avanzata (oltre la seconda CR o ricaduta/refrattarietà)	
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	PEDIATRICO: Neuroblastoma ad Alto Fischio	
	PEDIATRICO: Anemia a Cellule Falciformi*	
	Altro:	
	Altro:	

* Potenziali rischi associati

Note

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- 24-2-16 (+89) ricovero in Medicina generale per anemia acuta per melena, da piastrinopenia e gastrite emorragica, in corso di riattivazione CMV (ganciclovir e foscarnet)
- 27-2-16 addome disteso e dolente, aumento di peso con ascite.
- 29-2-16 ittero (bilirubina 3,3) e anasarca
- 1-3-16 cateterismo vene sovraepatiche: ipertensione portale sinusoidale severa con significativo gradiente transepatico cavale (IVC sovraepatica 3,1 intraepatica 11,3 e infraepatica 11,7)
- 1-3-16 agobiopsia epatica transgiugulare: marcata dilatazione sinusoidale con stavasi emorragici e eritrociti nello spazio di Disse. Marcata deposizione di ferro negli epatociti (grading istologico del ferro 3+) Quadro istologico coerente con SOS in fase acuta
- 2-3-16 (+95) Defibrotide 6,25 mg/kg x 4/die e.v per 3 settimane
- Recupero completo
- 19-9-18 ultimo follow up con pieno benessere

Mediterranean Journal of Hematology and Infectious Diseases

Case Report

Late-Onset Hepatic Veno-Occlusive Disease after Allografting: Report of Two Cases with Atypical Clinical Features Successfully Treated with Defibrotide

Alessia Castellino[1], Stefano Guidi[2], Chiara Maria Dellacasa[3], Antonella Gozzini[2], Irene Donnini[2], Chiara Nozzoli[2], Sara Manetta[3], Semra Aydin[1], Luisa Giaccone[3], Moreno Festuccia[3], Lucia Brunello[3], Enrico Maffini[3], Benedetto Bruno[3], Ezio David[4] and Alessandro Busca[3].

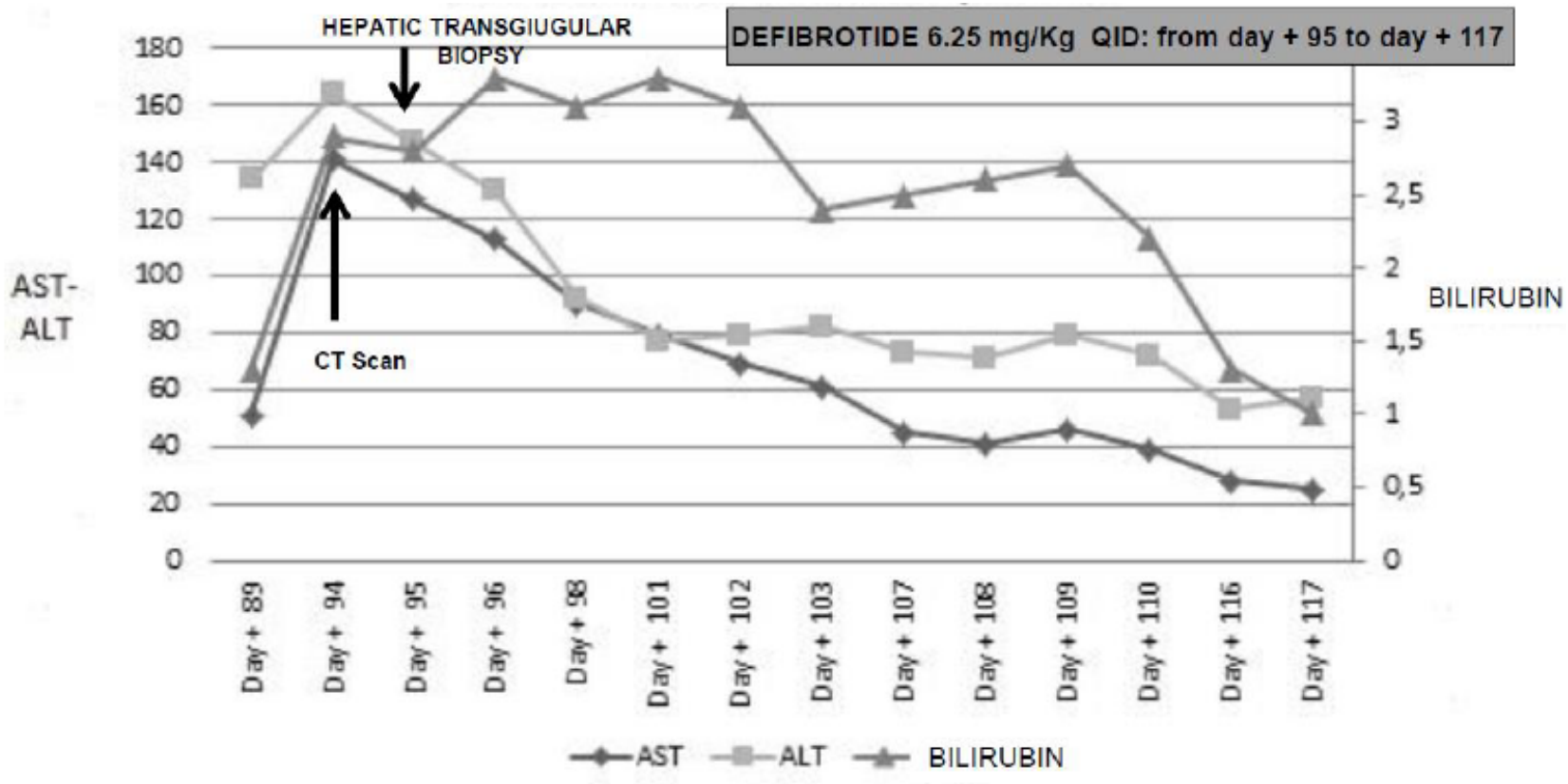

Figure 3. Diagnostic interventions with liver function profile from clinical onset of VOD until resolution, and treatment of VOD in case 2.

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Bilirubin kinetics			Doubling within 48 h	
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

Abbreviations: EBMT = European society for Blood and Marrow Transplantation; MOD = multi-organ dysfunction; MOF = multi-organ failure; SOS = sinusoidal obstruction syndrome; VOD = veno-occlusive disease. Patients belong to the category that fulfills two or more criteria. If patients fulfill two or more criteria in two 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. [a]In the case of presence of two or more risk factors for SOS/VOD, patients should be in the upper grade. [b]Patients with multi-organ dysfunction must be classified as very severe. [c]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.

Bone Marrow Transplantation (2016) **51,** 906–912

Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT)

M Mohty[1,32], F Malard[1,32], M Abecassis[2,32], E Aerts[3,32], AS Alaskar[4,32], M Aljurf[5,32], M Arat[6,32], P Bader[7,32], F Baron[8,32], A Bazarbachi[9,32], D Blaise[10,32], F Ciceri[11,32], S Corbacioglu[12,32], J-H Dalle[13,32], RF Duarte[14,32], T Fukuda[15,32], A Huynh[16,32], T Masszi[17,32], M Michallet[18,32], A Nagler[19,32], M NiChonghaile[20,32], T Pagluica[21,32], C Peters[22,32], FB Petersen[23,32], PG Richardson[24,32], T Ruutu[25,32], BN Savani[26,32], E Wallhult[27,32], I Yakoub-Agha[28,32] and E Carreras[29,30,31,32]

……..most accurate methods to confirm thediagnosis of SOS/VOD (measurement of the hepatic venous gradient pressure through the jugular vein, liver biopsy) are invasive and difficult to perform in routine practice…….

Bone Marrow Transplantation (2015) **50,** 781–789

Safety and Utility of Transjugular Liver Biopsy in Hematopoietic Stem Cell Transplant Recipients

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Purpose: Hematopoietic stem cell transplant (HSCT) recipients are at high risk in the setting of percutaneous liver biopsy as a result of comorbid coagulopathy and ascites, and are commonly referred to undergo transjugular liver biopsy. The present study was performed to assess the safety and utility of transjugular liver biopsy in HSCT recipients and to analyze the correlation between corrected hepatic sinusoidal pressure gradient (CHSPG) and pathologic diagnoses.

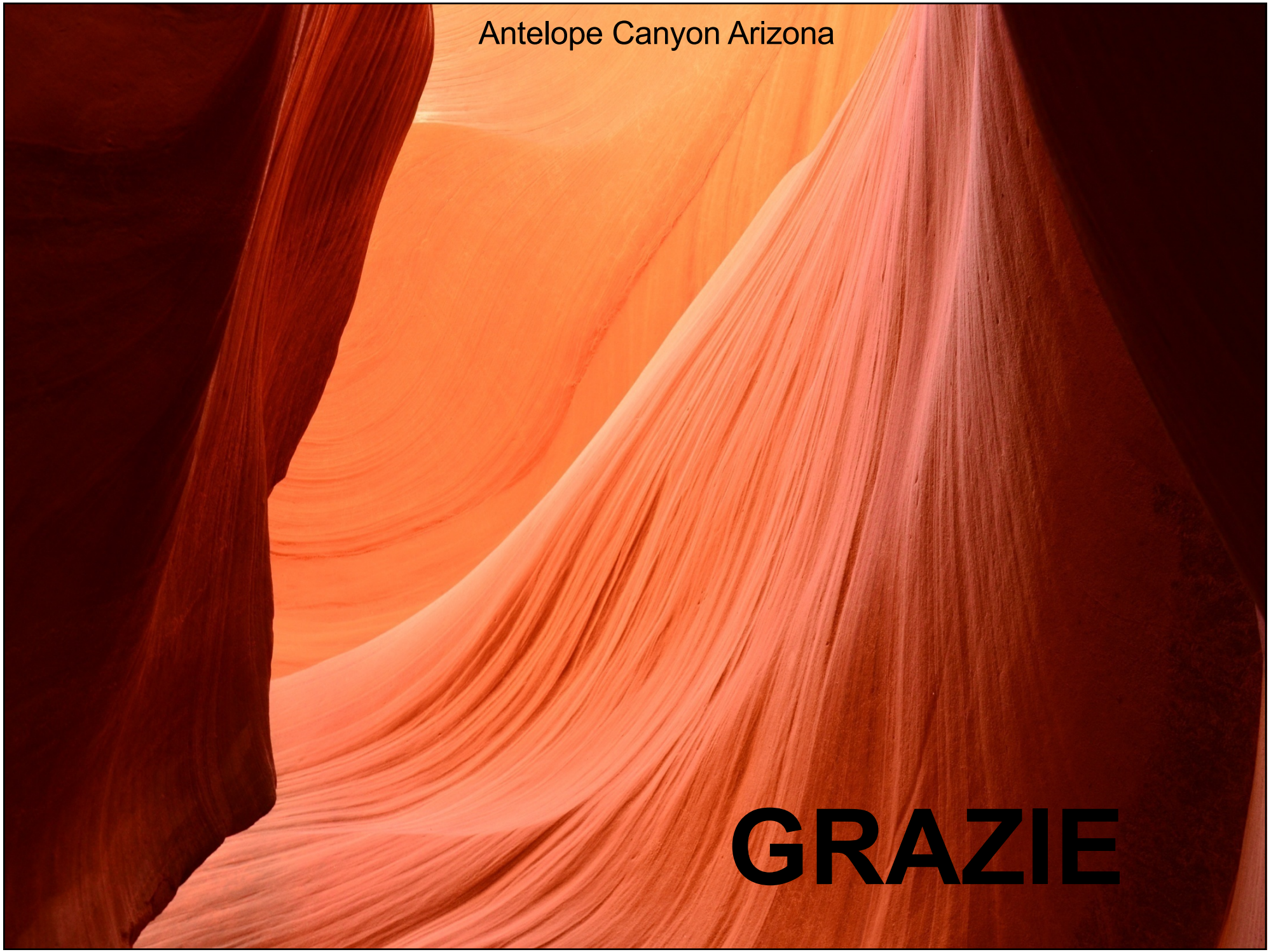
Materials and Methods: Data from reports of transjugular liver biopsy procedures, pathology reports, and laboratory values of 141 consecutive HSCT recipients who underwent transjugular liver biopsy with pressure measurement between January 2005 and August 2011 in a single institution were retrospectively reviewed and analyzed.

Results: A total of 166 biopsy procedures were performed in 141 patients. Technical success rate was 98.8%. Biopsy was diagnostic in 95.7% of patients. There were three major complications (1.8%), including one death. CHSPG in patients with venoocclusive disease (VOD) was significantly higher ($P < .001$) than in those without VOD (16.2 mm Hg ± 9.2 vs 5.6 mm Hg ± 3.7). A CHSPG of 10 mm Hg or higher was 90.8% specific and 77.3% sensitive for VOD.

Conclusions: The present data show that transjugular liver biopsy is a relatively safe procedure that provides important information for the clinical management of patients with HSCT. Measurement of CHSPG during the procedure can support the diagnosis of VOD.

Conclusioni

- La diagnosi precoce è essenziale
- Diagnosi mediante:
  - cateterismo diagnosi immediata
  - biopsia transgiugulare conferma
- Inizio del trattamento precoce
- Terapia efficace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