

GESTIONE DELLA VOD/SOS



Veronica Tintori
Trapianto di Cellule Staminali Emopoietiche, AOU MEYER

**Insorgenza
nei primi 20 gg dal
TCSE, ma possibile
di esordio più
tardivo**

**Complicanza
precoce del TCSE**

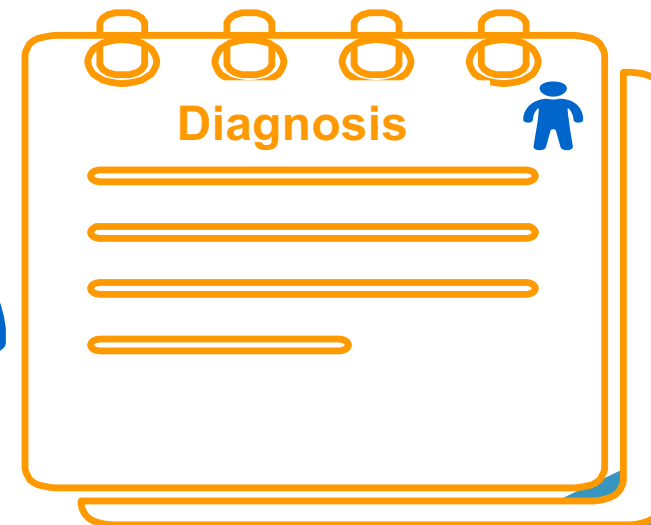
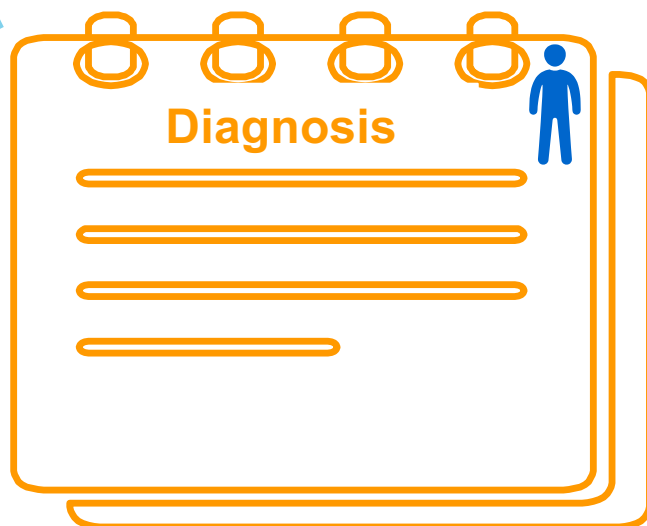
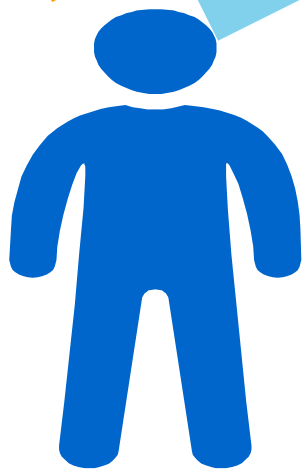
**Incidenza media
del 14%**

VOD/SOS

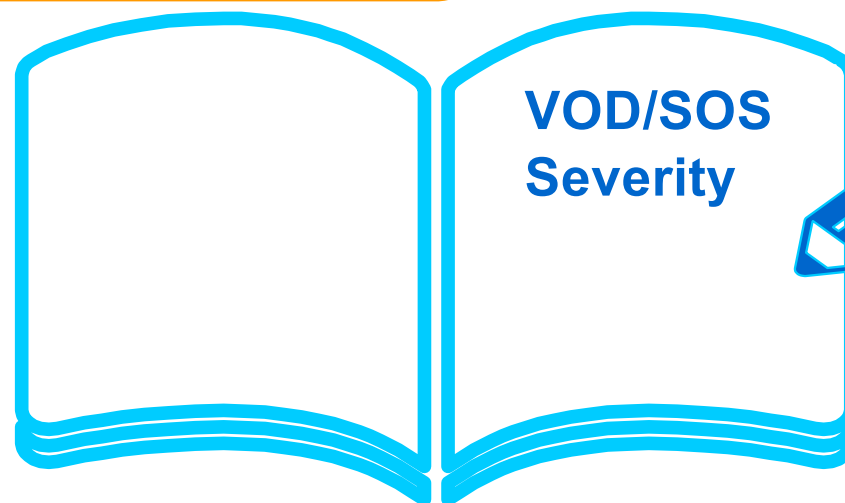
**Danno tossico del
condizionamento
sull'endotelio**

**In 1/3 dei casi
evolve in MOF e ha
una mortalità >80%**

VOD/SOS : nuovi criteri diagnostici e prognostici



***Mothy et al, Bone
Marrow Transplant 2016***



***Corbacioglu et al, Bone
Marrow Transplant 2016***

VOD/SOS : bambino vs adulto



Incidenza 20%

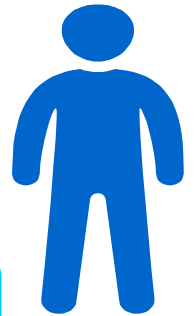
20-30% Forme late-onset e anitteriche

Elevati fattori di rischio per età e patologia di base

Frequente insorgenza se epatopatia pregressa

Migliore risposta al trattamento

Ridotta incidenza con profilassi



Incidenza 10%

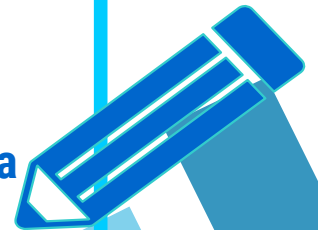
Forme late-onset e anitteriche rare

Fattori di rischio generici

Minore insorgenza se epatopatia pregressa

Minore risposta al trattamento

Trial clinico in corso



VOD/SOS : non malattia orfana, ma suscettibile di trattamento





TERAPIA

✓ TERAPIA DI SUPPORTO

- Diuresi forzata per ridurre ritenzione idrica mantenendo perfusione renale;
- Correzione della coagulopatia;
- Analgesia;
- O2 terapia o supporto ventilatorio
- Paracentesi
- Tp antibiotica

✓ TERAPIA ANTITROMBOTICA

t-PA (Tissue-pasminogen activator) per promuovere la fibrinolisi con elevato rischio di complicanze emorragiche

✓ TERAPIA STEROIDEA

Metilprednisolone ad alte dosi ha dimostrato una discreta efficacia



Defibrotide

- **2013** approvato da EMA per utilizzo in VOD/SOS severa in EU
- **2016** approvato da FDA per utilizzo in VOD/SOS con complicanze renali e polmonari negli USA



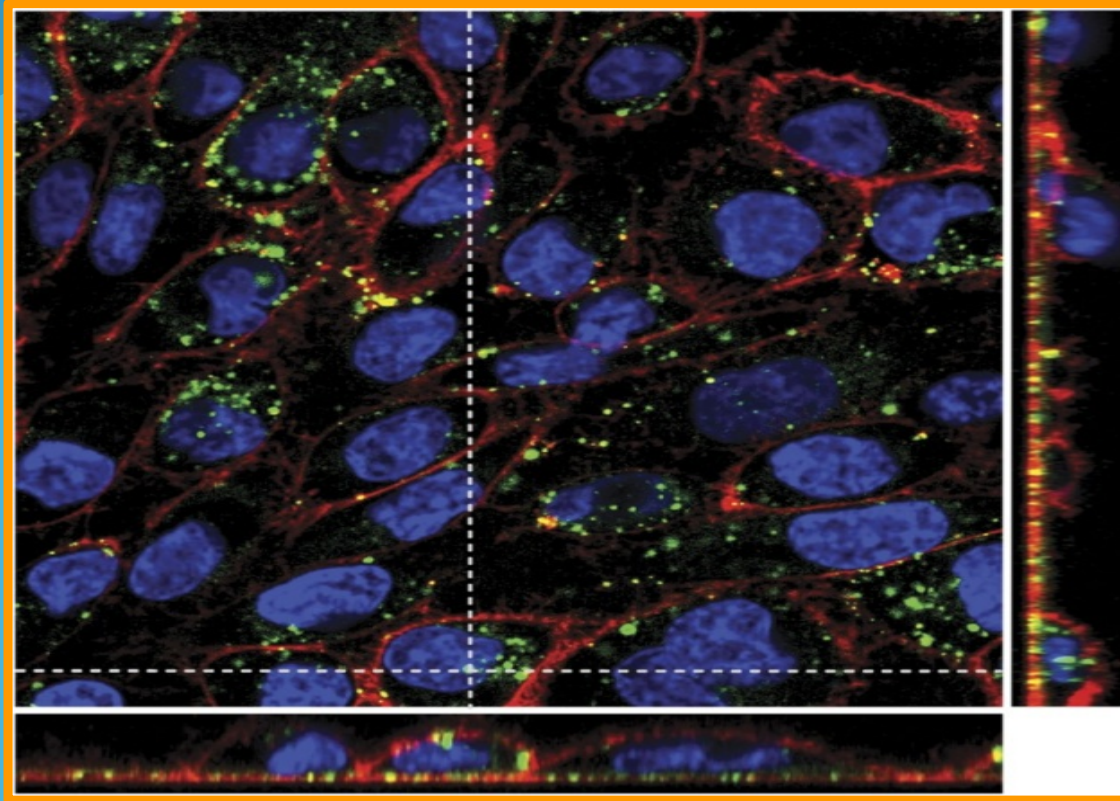
DEFIBROTIDE

Dosaggio: 6,25 mg/kg
in infusione ev di 2 ore ogni 6 ore

- Effetto anti-trombotico
- Effetto anti-ischemico
- Effetto anti-infiammatorio
- Effetto angio-protettivo

Morabito, Expert Opin Biol Ther, 2009

What is going on between defibrotide and endothelial cells? Snapshots reveal the hot spots of their romance



Palomo et al, Blood 2016

EFFICACIA CLINICA

CLINICAL TRIAL	STUDY DESIGN	PATIENT NUMBER	RESULTS
RICHARDSON BIOL BLOOD MARROW TRANSPLANT, 2010	PHASE II PROSPECTIVE RANDOMIZED DOSE FINDING STUDY	N = 149	DAY+100 SURVIVAL: 44% (95%CI :33%, 55%)
RICHARDSON, BLOOD 2016	PHASE III PROSPECTIVE STUDY	N = 102	DAY +100 SURVIVAL: 38% (95%CI :29%, 48%)
KERNAN BR J HAEMATOLOGY. 2018	PHASE III PROSPECTIVE EXPANDED ACCESS	N = 1000	DAY +100 SURVIVAL 58,9% (95% CI: 55,7%, 61,9%) 67,9% PEDIATRICS 47,1% ADULTS

NO SERIOUS AEs / TRAEs IN ALL THREE TRIALS

Phase 3 study

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

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

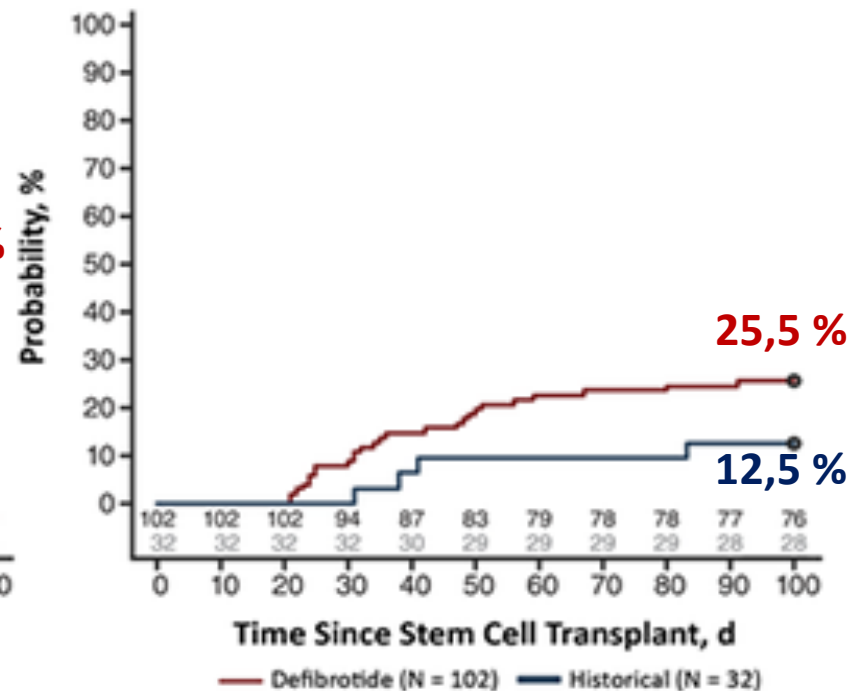
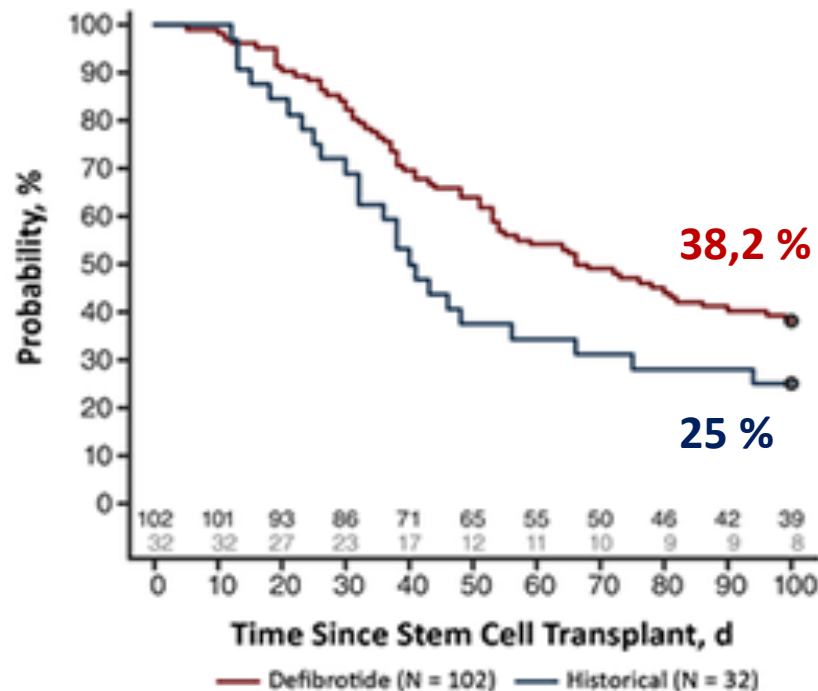
Paul G. Richardson,¹ Marcie L. Riches,² Nancy A. Kernan,³ Joel A. Brochstein,⁴ Shin Mineishi,⁵ Amanda M. Termuhlen,⁶ Sally Arai,⁷ Stephan A. Grupp,⁸ Eva C. Guinan,^{1,9} Paul L. Martin,¹⁰ Gideon Steinbach,¹¹ Amrita Krishnan,¹² Eneida R. Nemecek,¹³ Sergio Giralte,¹⁴ Tulio Rodriguez,¹⁵ Reggie Duerst,¹⁶ John Doyle,¹⁷ Joseph H. Antin,¹ Angela Smith,¹⁸ Leslie Lehmann,^{1,9} Richard Champlin,¹⁹ Alfred Gillio,²⁰ Rajinder Bajwa,²¹ Ralph B. D'Agostino Sr.,²² Joseph Massaro,²² Diane Warren,¹ Maja Miloslavsky,²³ Robin L. Hume,²⁴ Massimo Iacobelli,²⁵ Bijan Nejadnik,²⁶ Alison L. Hannah,²⁷ and Robert J. Soiffer¹

¹Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; ²Division of Hematology/Oncology, University of North Carolina Hospitals, Bone Marrow and Stem Cell Transplant Clinic, University of North Carolina Cancer Hospital, Chapel Hill, NC; ³Pediatric Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, New York, NY; ⁴Department of Pediatrics, Stem Cell Transplant Program, Cohen Children's Medical Center, New Hyde Park, NY; ⁵Division of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL; ⁶Division of Pediatric Hematology, Oncology, Blood and Marrow Transplantation, Children's Hospital Los Angeles, Los Angeles, CA; ⁷Blood and Marrow Transplantation, Stanford University Medical Center, Stanford, CA; ⁸Pediatric Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA; ⁹Department of Hematology/Oncology, Children's Hospital, Boston, MA; ¹⁰Division of Pediatric Blood and Marrow Transplant, Duke University Medical Center, Durham, NC; ¹¹Gastroenterology Division, University of Washington School of Medicine and Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; ¹²Department of Hematology & Hematopoietic Cell Transplantation, City of Hope, Duarte, CA; ¹³Pediatric Bone Marrow Transplant Program, Oregon Health and Science University, Portland, OR; ¹⁴Adult Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, New York, NY; ¹⁵Hematology/Oncology, Loyola University Medical Center, Chicago, IL; ¹⁶Stem Cell Transplant Program, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; ¹⁷Pediatric Hematology/Oncology, CancerCare Manitoba and the University of Manitoba, Winnipeg, Manitoba, Canada; ¹⁸Division of Blood and Marrow Transplantation, University of Minnesota, Minneapolis, MN; ¹⁹Department of Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, The University of Texas, Houston, TX; ²⁰Department of Pediatrics, Hackensack University Medical Center, Hackensack, NJ; ²¹Department of Hematology/Oncology/BMT, The Ohio State University/Nationwide Children's Hospital, Columbus, OH; ²²Department of Mathematics and Statistics, Boston University, Boston, MA; ²³Biostatistics, Jazz Pharmaceuticals, Palo Alto, CA; ²⁴Regulatory Affairs, Jazz Pharmaceuticals, Palo Alto, CA; ²⁵Life Sciences, Techint Srl, Milano, Italy; ²⁶Research and Clinical Development, Galena Biopharma, San Ramon, CA; and ²⁷Clinical Operations, Jazz Pharmaceuticals, Palo Alto, CA

Fase III Defibrotide in VOD/SOS severa

Outcomes al giorno 100, defibrotide vs braccio di controllo

- Sopravvivenza: 38,2% vs 25% (23% differenza; $P = .0109$)
- RC 25,5% vs 12,5% (19% differenza; $P = .01060$)



Richardson et al, Blood 2016

T-IND study

WILEY

BRITISH JOURNAL OF HAEMATOLOGY

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[Br J Haematol.](#) 2018 Jun; 181(6): 816–827.

PMCID: PMC6032999

Published online 2018 May 16. doi: [\[10.1111/bjh.15267\]](https://doi.org/10.1111/bjh.15267)

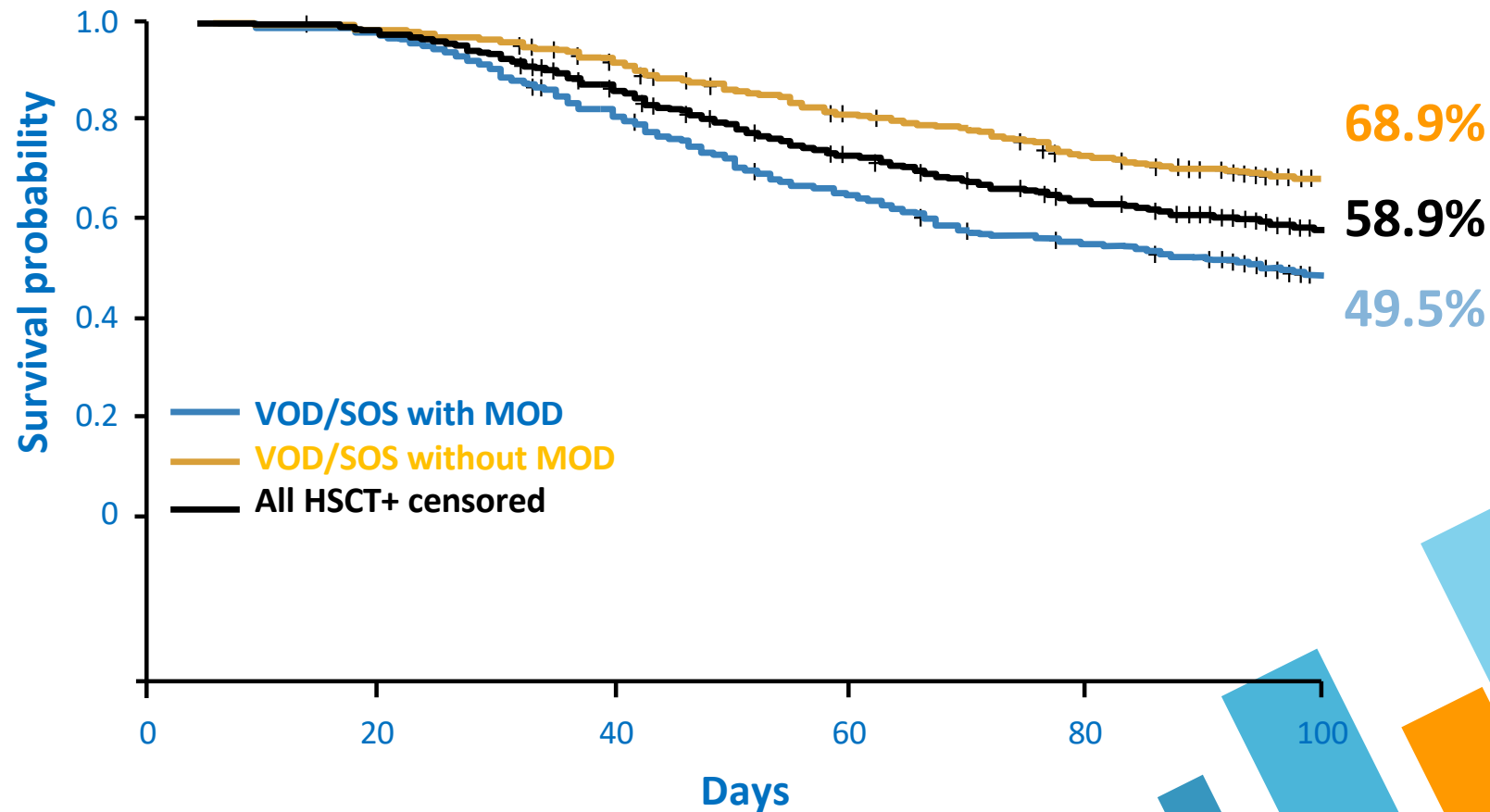
PMID: [29767845](https://pubmed.ncbi.nlm.nih.gov/29767845/)

Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome

[Nancy A. Kernan](#),¹ [Stephan Grupp](#),² [Angela R. Smith](#),³ [Sally Arai](#),⁴ [Brandon Triplett](#),⁵ [Joseph H. Antin](#),⁶ [Leslie Lehmann](#),⁶ [Tsiporah Shore](#),⁷ [Vincent T. Ho](#),⁶ [Nancy Bunin](#),² [Massimo Iacobelli](#),⁸ [Wei Liang](#),⁹ [Robin Hume](#),⁹ [William Tappe](#),⁹ [Robert Soiffer](#),⁶ and [Paul Richardson](#)⁶

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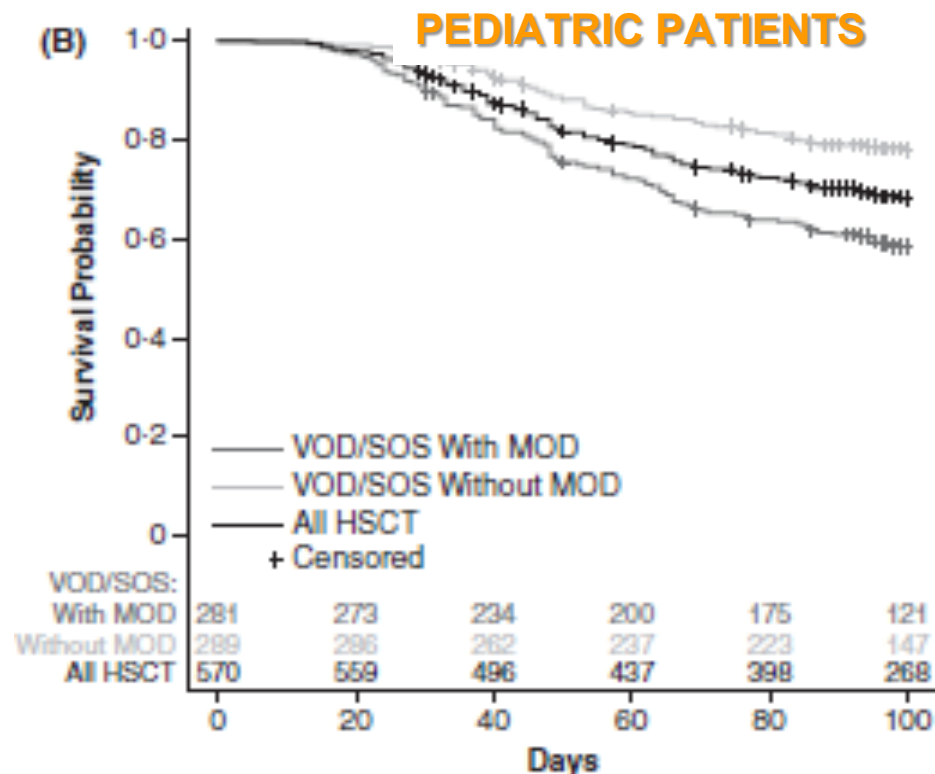
Results: Kaplan–Meier estimated Day +100 survival in patients with SOS/VOD after HSCT (1000 patients)



Kernan NA, et al. Br J Haematol 2018;

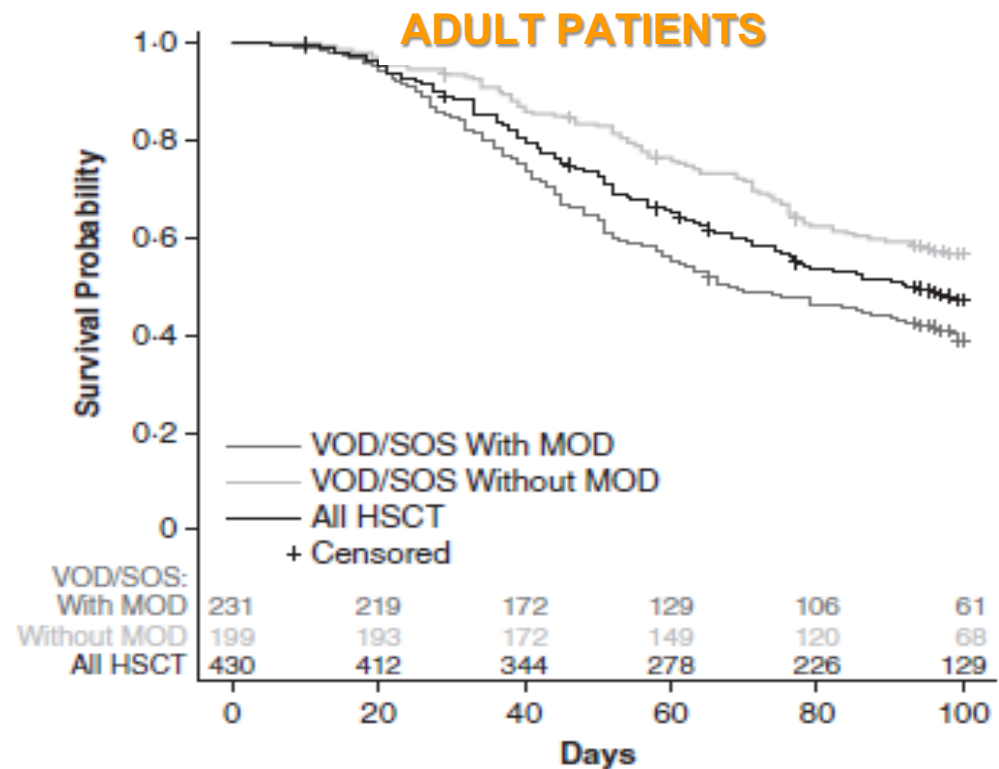
Results: OS in paediatric and adult patients

Kaplan-Meier estimated survival to Day +100 by age status:



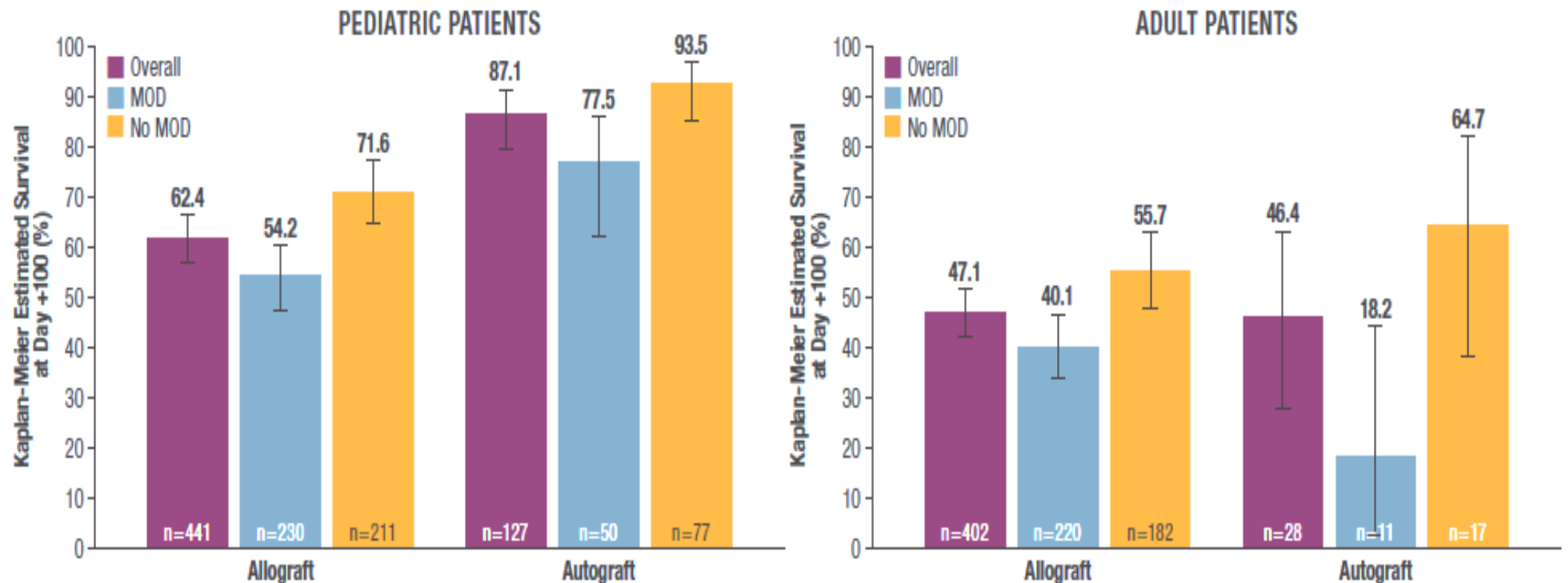
67.9% OS

Kernan NA, et al. Br J Haematol 2018;



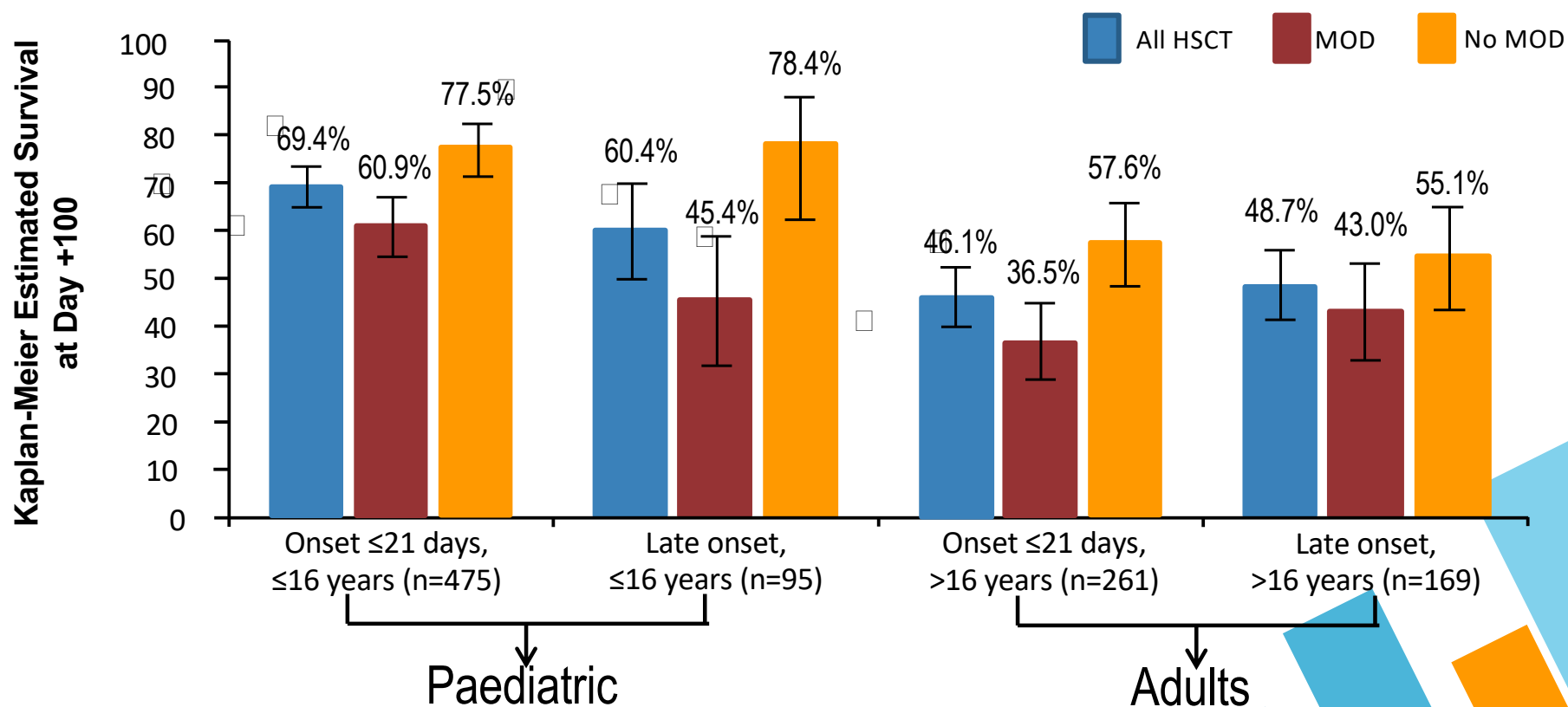
47.1% OS

Results: Kaplan-Meier Day +100 Survival of VOD/SOS Patients Post-HSCT by Graft Type and Age Category



Kernan NA, et al. Br J Haematol 2018;

Results: Kaplan–Meier estimated Day +100 survival by time of SOS/VOD onset post-HSCT



Kernan NA, et al. Br J Haematol 2018;

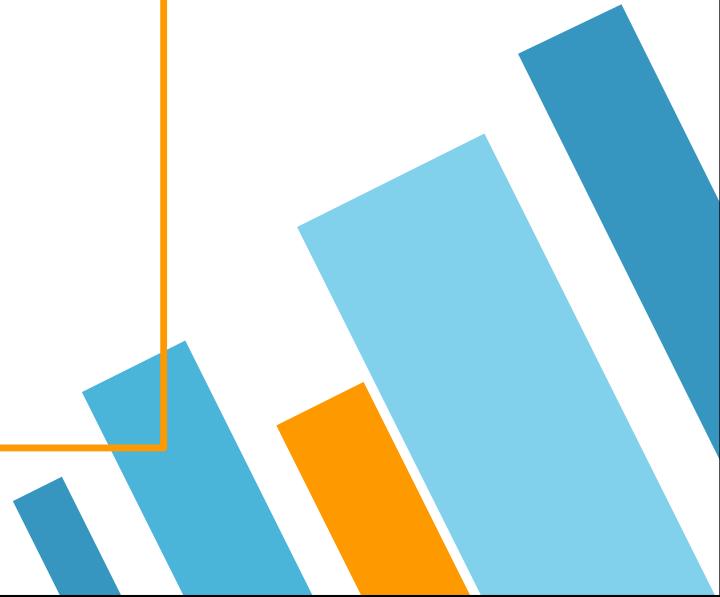


ALTRE TERAPIE PER VOD/SOS SEVERA

Sintomatiche

- Analgesia
- Paracentesi
- Emodialisi/emofiltrazione
- Ventilazione meccanica

Specifiche

- Shunt porto-sistemico
 - Trapianto di fegato
- 

Gestione della VOD/SOS



Fattori di
rischio

Test
diagnostici
precoci

Profilassi

**Terapia
precoce**

Terapia



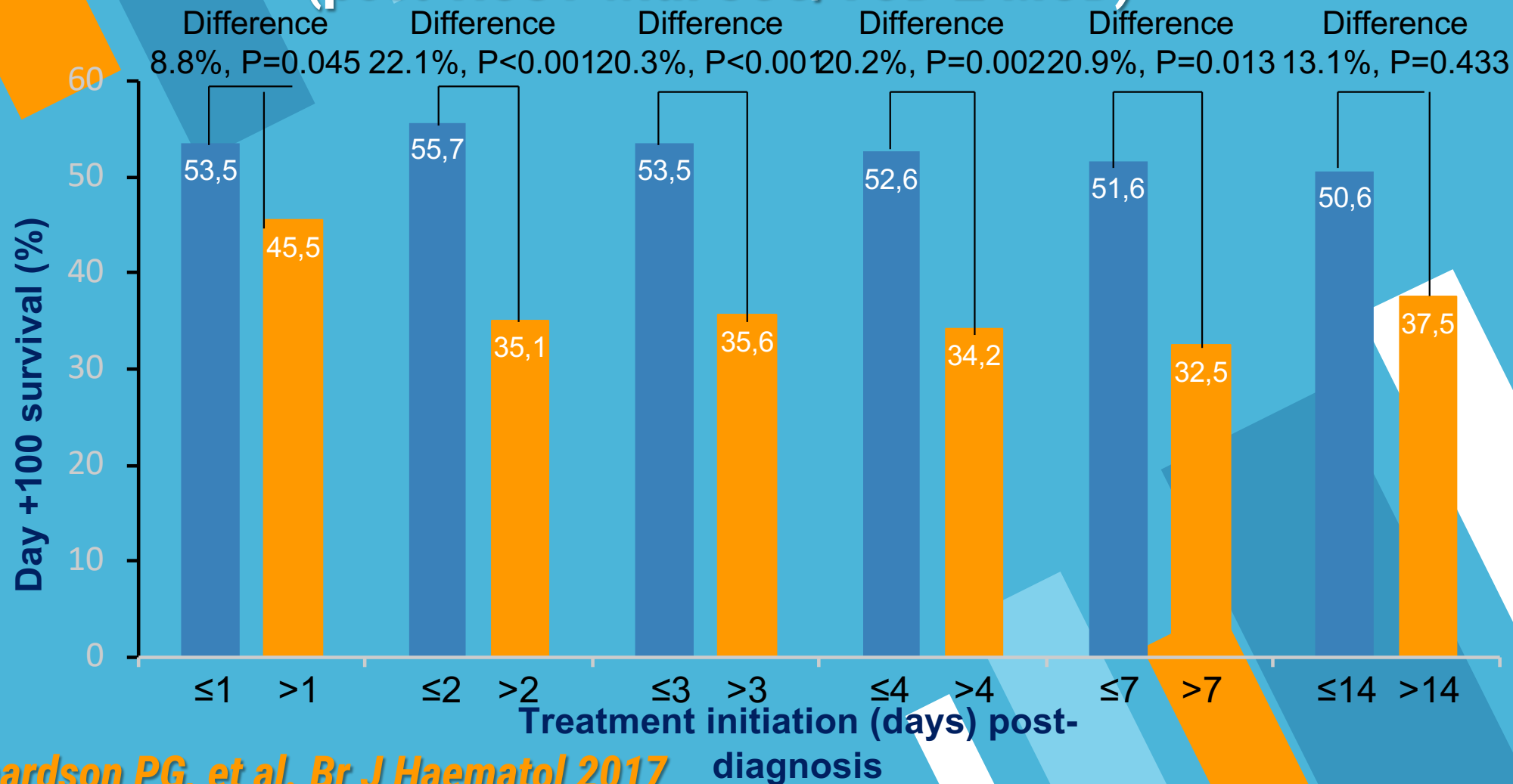
Research Paper |  Open Access |   

Earlier defibrotide initiation post-diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome improves Day +100 survival following haematopoietic stem cell transplantation

Paul G. Richardson , Angela R. Smith, Brandon M. Triplett, Nancy A. Kernan, Stephan A. Grupp, Joseph H. Antin, Leslie Lehmann, Maja Miloslavsky, Robin Hume, Alison L. Hannah, ... [See all authors](#) 

First published: 26 April 2017 | <https://doi.org/10.1111/bjh.14727> | Cited by: 11

Results: Day +100 survival by defibrotide initiation day (post-HSCT with SOS/VOD $\pm$ MOD)



Richardson PG, et al. Br J Haematol 2017

Gestione della VOD/SOS



Fattori di
rischio

Test
diagnostici
precoci

Profilassi

**Terapia
precoce**

Terapia

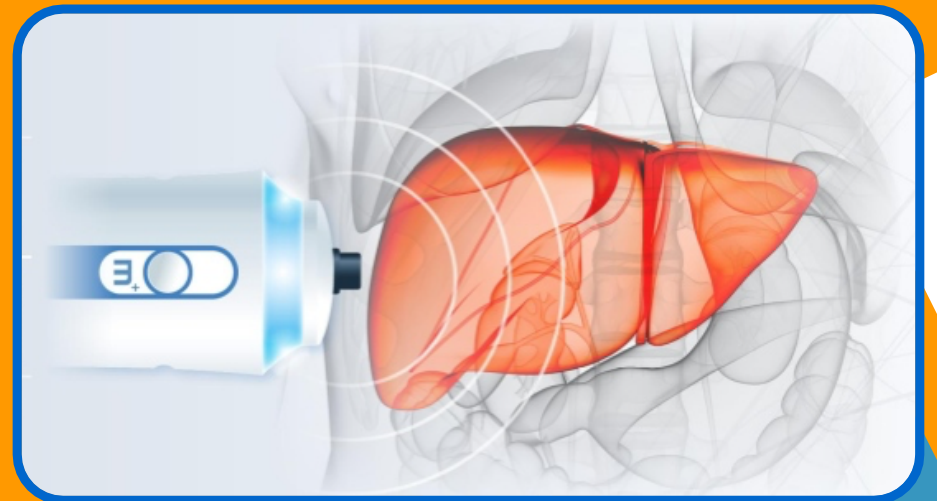


E' possibile una terapia pre-emptive?

**Dosaggio di
markers endoteliali**

**L-Ficolin, VCAM1,
HA, vWF, ICAM1,
thrombomodulina**

Ecografia e Fibroscan



Profilassi

```
graph TD; A[Profilassi] --> B[Reversione dei fattori di rischio]; A --> C[Intervento farmacologico];
```

Reversione dei
fattori di rischio

Intervento
farmacologico

FATTORI DI RISCHIO

Transplant related	Patient/disease related	Hepatic related	Pediatric Specific
Allo-HSCT>auto-HSCT	Older>younger (in adult patients)	Transaminase>2.5 ULN Serum bilirubin >1.5 ULN	HLH
Unrelated donor	Female receiving norethisterone	Cirrhosis	Adrenoleucodystrophy,
HLA-mismatched donor	Karnofsky score below 90%	Hepatic fibrosis	Osteopetrosis
Myeloablative conditioning regimen	Gene polymorphism (GSTM1, GSTMT1, heparanase)	Active viral hepatitis	High-dose auto-HSCT in neuroblastoma
BU-based conditioning regimen	Advanced disease (beyond second CR or relapse)	Hepatic irradiation	Young age (under 1–2 years of age)
TBI-based conditioning regimen	Metaboic syndrome	Previous use of gemtuzumab ozogamicin/ inotuzumab	Low weight
Non-T-cell-depleted graft	Deficit of AT III, t-PA and resistance to activated protein C	Use of hepatotoxic drugs	Juvenile myelo-monocytic chronic leukemia
Second HSCT	Thalassemia	Iron overload	

PROFILASSI FARMACOLOGICA

Anticoagulants (sodium heparin, LMWH)¹; antithrombin¹; prostaglandin E1¹; pentoxifylline¹



Inconclusive, mixed, or negative efficacy results and bleeding risk → NOT recommended

Ursodiol¹⁻³



Meta-analysis demonstrated overall reduction in VOD incidence

↑
Included in guidelines for prophylaxis (BCSH/BSBMT)

↓
Defibrotide^{2,4,5}

Phase 3 study of DF prophylaxis in adults ongoing⁴



In pediatric HSCT recipients, lower incidence of VOD/SOS but no difference in overall survival³

THE LANCET

ARTICLES | [VOLUME 379, ISSUE 9823, P1301-1309, APRIL 07, 2012](#)

Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial

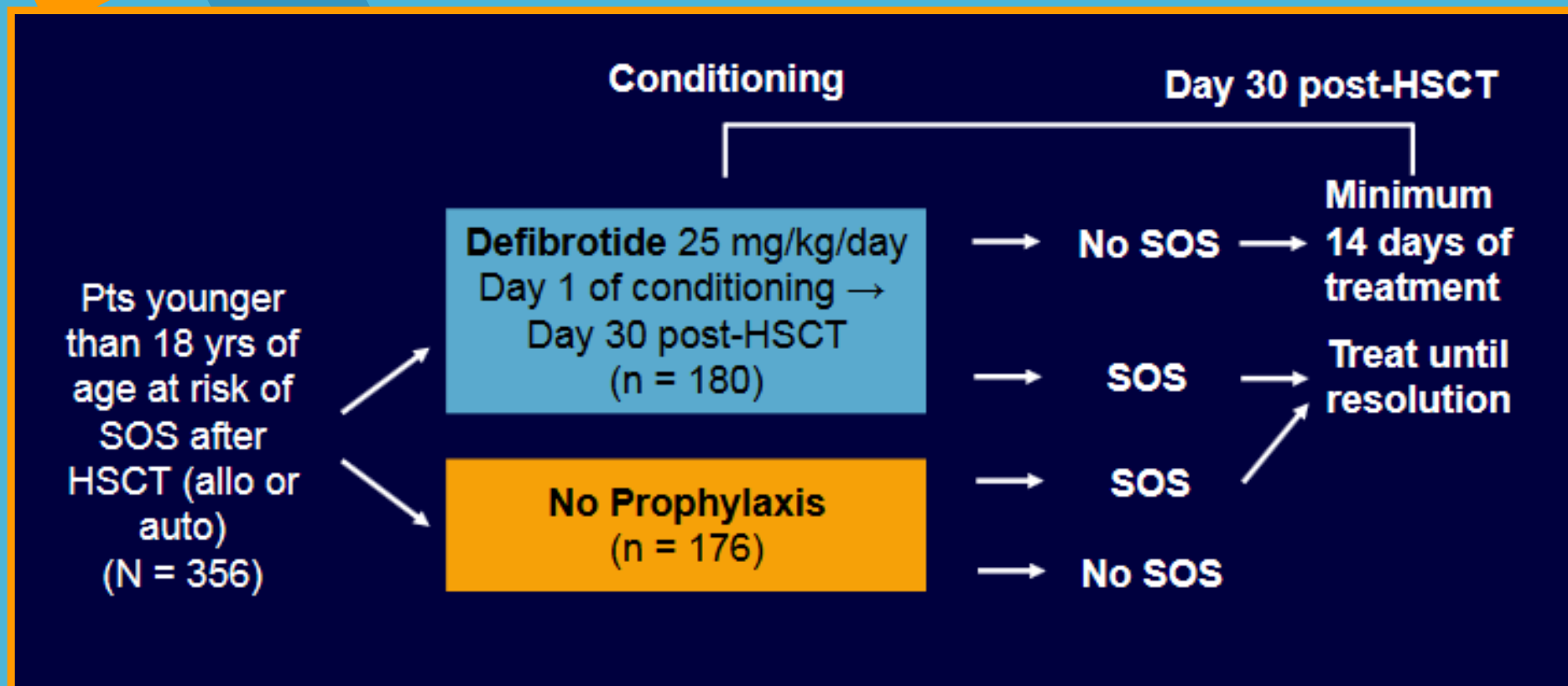
[Prof Selim Corbacioglu, MD](#)   • [Simone Cesaro, MD](#) • [Maura Faraci, MD](#) • [Dominique Valteau-Couanet, MD](#) •

[Bernd Gruhn, MD](#) • [Attilio Rovelli, MD](#) • et al. [Show all authors](#) • [Show footnotes](#)

Published: February 23, 2012 • DOI: [https://doi.org/10.1016/S0140-6736\(11\)61938-7](https://doi.org/10.1016/S0140-6736(11)61938-7)

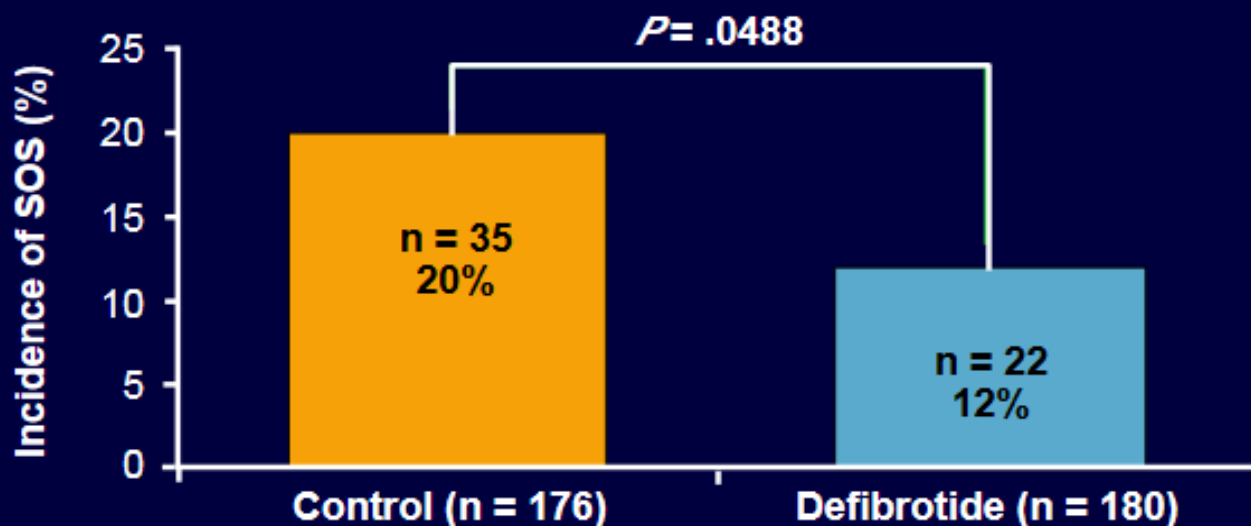
127 received
in the safe
18 not

Phase III EBMT Pediatric Trial: Defibrotide as SOS/VOD prophylaxis after HSCT



Corbacioglu et al, Lancet 2012

Phase III EBMT Pediatric Trial: Defibrotide as SOS/VOD prophylaxis after HCST



- No significant difference in SOS-associated mortality at 100 days after HSCT: 2% with defibrotide vs 6% in control group ($P = .10$)
- However, mortality at 100 days was 4 times higher in pts with vs without SOS (25% vs 6%; $P < .0001$)

Corbacioglu et al, Lancet 2012

Defibrotide in profilassi è off-label





Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org



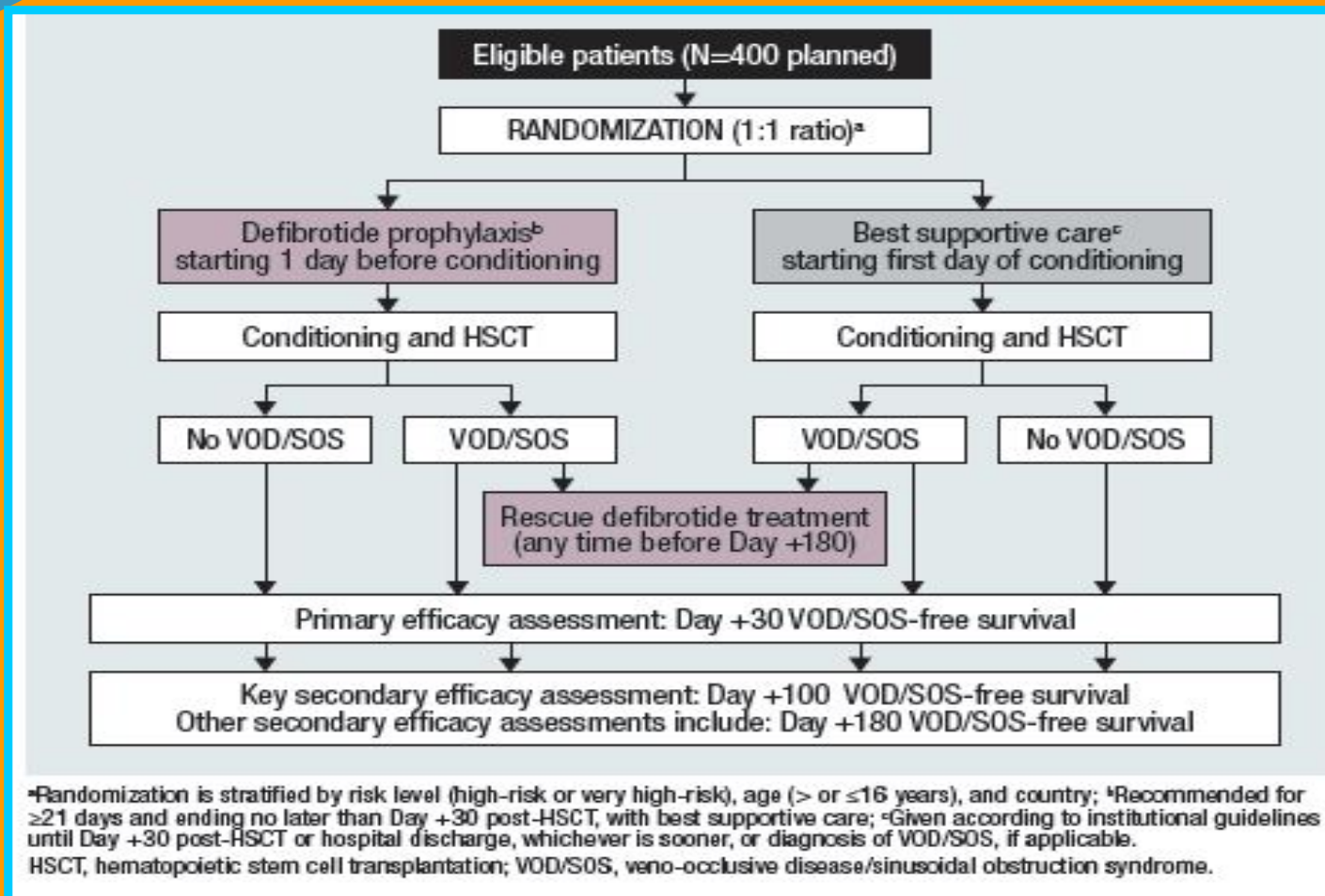
Cost-Effectiveness of Defibrotide in the Prophylaxis of Veno-Occlusive Disease after Pediatric Allogeneic Stem Cell Transplantation



Herbert Pichler ^{1,*}, Karolina Horner ¹, Gernot Engstler ¹, Ulrike Poetschger ², Evgenia Glogova ², Susanne Karlhuber ², Manuel Martin ³, Werner Eibler ¹, Volker Witt ¹, Wolfgang Holter ¹, Susanne Matthes-Martin ¹

- Il costo mediano di un trapianto con VOD è di 188.744 € vs 136.382 € costo mediano dei precedenti trapianti. Il costo incrementale per i 26 pz con VOD è di 1.361.412 €
- Il costo della profilassi per i 148 pz a rischio, calcolata moltiplicando 81 €/kg di peso del paziente per i giorni di trattamento è di 8.088.616 €
- Calcolando che il NNT in questa coorte è 12, il costo per prevenire 1 caso di VOD è di 703.00 €, quindi economicamente non sostenibile.

PHASE 3, RANDOMIZED TRIAL OF DEFIBROTIDE FOR PREVENTION OF VOD/SOS



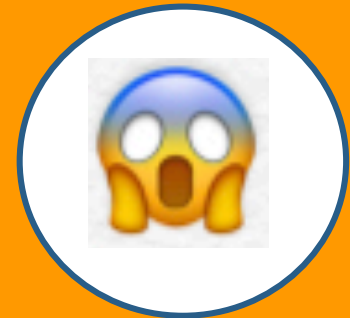
E tu come gestisci la VOD/SOS?



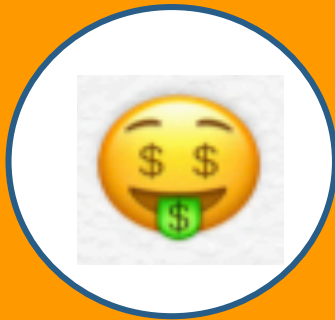
Il temerario



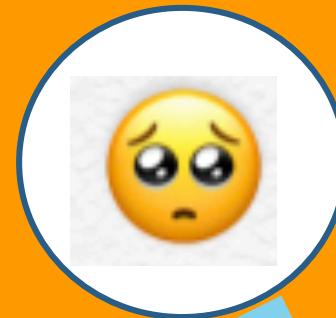
Il diligente



Il catastrofista



Il parsimonioso



Il pusillanime

Paziente candidato a TCSE auto o allo

VOD Assessment Risk

Fattore di rischio ²	OR <3	Fattore di rischio ²	OR = 3-10	Fattore di rischio ²	OR >10
Mielodisplasia concomitante	1,5	Febbre/nutr. parenterale/diarrea prima del trapianto	2,9/3,0/3,2	Trattamento con noretisterone	10,1
Errori congeniti metabolismo	1,8	Livelli ferritina >1000 ng/ml	3,1	Trattamento con gemtuzumab ozogamicina	19,8
Pregresso TCS	1,9	Immunodeficienza concomit.	3,3	Bilirubina >26 µmol/l prima del TMO	23,5
Leucemia (LMC) concomit.	2,2 (3,0)	Epatopatia preesistente	3,4		
Vancomicina durante terapia citoriduttiva	2,4	Talassemia concomitante	4,0		
Compr. funzione polmonare	2,4	Sepsi	4,1		
Scarso performance status (Karnofsky <90%)	2,7	Fattori genetici (genotipo GSTM1 null)	4,1		
Irradiazione dell'addome	2,9	Aumento livelli transaminasi	2,4-4,6		
		Aciclovir pretrapianto	4,8		
		Età	5,2-9,5		

Adattato da Dalle J-H, Giralt SA 2015²

Fattore di rischio ¹	OR <3	Fattore di rischio ¹	OR = 3-10
TCS da sangue periferico versus TMO	1,3	Profilassi della GvHD	3-4,2
Donatore non consanguineo/non compatibilità HLA	1,4	Terapia a dosi elevate/mieloablative	2,3-7,9
GvHD acuta epatica/intestinale	-2,0		
Trapianti non T-depleti	2,2		
>12 mesi tra diagnosi e trapianto	2,3		
Irradiazione corporea totale a dosi elevate	2,8		
TCS allogenico versus autologo	2,8		

Adattato da Dalle J-H, Giralt SA 2015²

OR = odds ratio per lo sviluppo della VOD in confronto agli "odds" in assenza di esposizione al fattore di rischio.

Basso
Rischio

Monitoraggio
clinico

Inizio trattamento in
presenza dei criteri
diagnostici

Alto
rischio

Stretto monitoraggio
clinico e Fibroscan

Inizio trattamento in
presenza di criteri
diagnostici

Altissimo
rischio

Profilassi off-label
da -1 a +21

Prosegue il trattamento
in presenza di criteri
diagnostici

“Meyer Transplant Team”



Prof. Gambineri



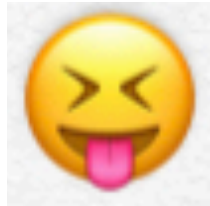
Dr. Favre



Dr.ssa Cuzzubbo



Dr. Frenos



Dr.ssa Tintori



Dr.ssa Sanvito

Grazie per l'attenzione!