Veno-occlusive disease (VOD/SOS) in BMT – the role of the nephrologist

Shirley Pollack, Roni Gefen

Pediatric Nephrology Unit

Pediatric Bone Marrow Transplantation Unit

Ruth Children Hospital, Rambam Medical Center, Haifa

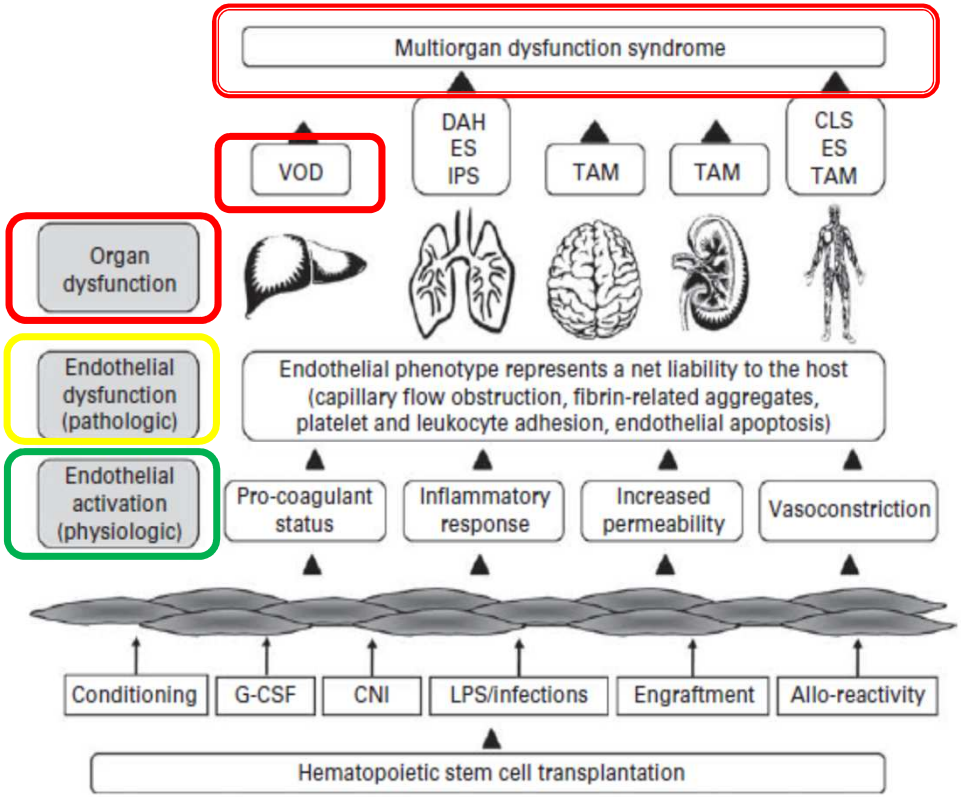
ISPN & ISPHO - 20.11.2019

רות
בית חולים רות רפפורט לילדים
רמב"ם-הקריה הרפואית לבריאות האדם

רמב"ם מרכז רפואי
אקדמי מצטיין

Veno-occlusive disease / sinusoidal obstruction syndrome

- An endothelial injury leading to liver damage & multi organ failure



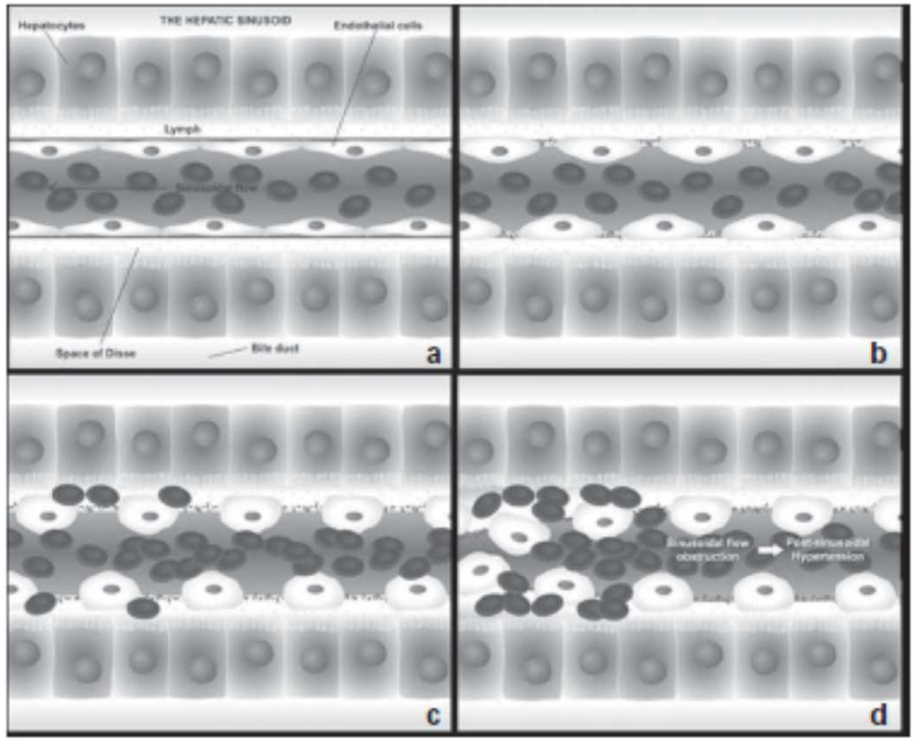
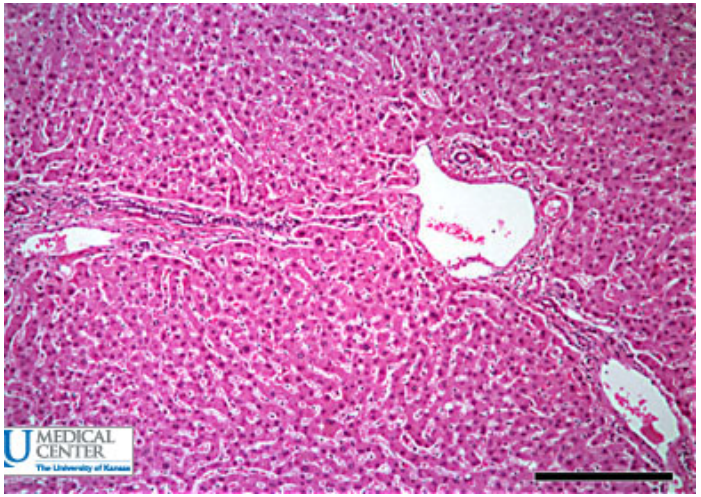
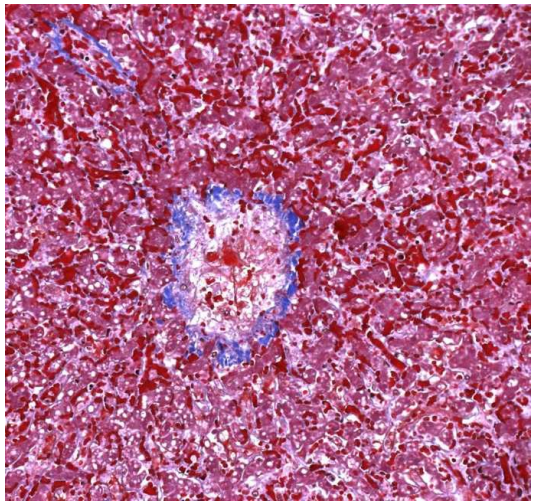


Figure 2 Common pathogenesis of the vascular endothelial syndromes developed early after HSCT. CLS, capillary leak syndrome; CNI, cal inhibitors; DAH, diffuse alveolar haemorrhage; ES, engraftment syndrome; IPS, idiopathic pneumonia syndrome; LPS, lipopolysaccharide; TAM, transplant-associated microangiopathy; VOD, veno-occlusive disease.

Carreras E, Diaz-Ricart M. *Bone Marrow Transplant* 2011;46:1495–502

- Clinically presents with:
  - Weight gain
  - Tender hepatomegaly & ascites
  - Jaundice





VOD/SOS
Differences between children and adults

Table 1. Major differences in hepatic SOS/VOD between adults and children

Criteria	*Children*	*Adults*
Incidence	• Approximately 20% • Up to 60% in high-risk patients	• Approximately 10%
Risk factors	Additional pediatric risk factors: • Infants • Pediatric/genetic diseases with incidences above average	• Established risk factors
Clinical presentation	• Late-onset SOS/VOD in 20% • Anicteric SOS/VOD in 30% • Hyperbilirubinemia, if present: ○ Is frequently pre-existent ○ Occurs late during SOS/VOD ○ Is typical of severe SOS/VOD	• Late-onset SOS/VOD is rare • Anicteric SOS/VOD is rare
Need for proper assessment of ascites and hepatomegaly	• High incidence of disease-related hepatomegaly and ascites pre-HCT	
Treatment	• DF for severe SOS/VOD with MOD/MOF was associated with better results in children compared with adults	
Prevention	• DF demonstrated efficacy for prevention of SOS/VOD in children in a randomized prospective trial	

Abbreviations: DF = defibrotide; HCT = hematopoietic cell transplantation; MOD/MOF = multi-organ dysfunction/multi-organ failure; SOS/VOD = sinusoidal obstruction syndrome/veno-occlusive disease.

S Corbacioglu et al. *Bone Marrow Transplant* 2018;53:138–145

VOD/SOS diagnosis
Newest EBMT criteria

Table 2. EBMT diagnostic criteria for hepatic SOS/VOD in children

- No limitation for time of onset of SOS/VOD

The presence of two or more of the following[a]

- Unexplained consumptive and transfusion-refractory thrombocytopenia[b]
- Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain $>5\%$ above baseline value
- [c]Hepatomegaly (best if confirmed by imaging) above baseline value
- [c]Ascites (best if confirmed by imaging) above baseline value
- Rising bilirubin from a baseline value on 3 consecutive days or bilirubin $\geqslant 2$ mg/dL within 72 h

Abbreviations: CT = computed tomography; HCT = hematopoietic cell transplantation; MRI = magnetic resonance imaging; SOS/VOD = sinusoidal obstruction syndrome/veno-occlusive disease; US = ultrasonography. [a]With the exclusion of other potential differential diagnoses. [b]$\geqslant 1$ weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines. [c]Suggested: imaging (US, CT or MRI) immediately before HCT to determine baseline value for both hepatomegaly and ascites.

S Corbacioglu et al. *Bone Marrow Transplant* 2018;53:138–145

VOD in pediatric HSCTs: The Rambam experience

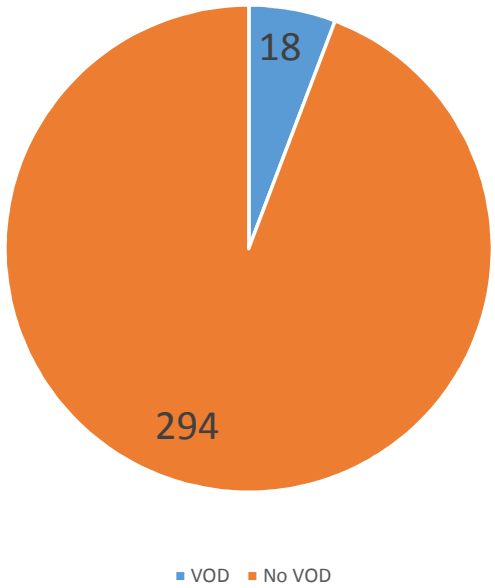
- Retrospective cohort of Pediatric HSCTs
  - January 2005 – May 2019

- Definition of VOD based on:
  - Review of computerized charts
  - Discharge diagnosis of VOD
  - New EBMT or Baltimore / Modified Seattle criteria

VOD in pediatric HSCTs 2005-2019

- **VOD** diagnoses: **20**
  - Oncologic patients w/o HSCT: 2
- VOD & HSCT for analysis: **18**
  - Allo: 9 (50%)
  - Auto: 9
  - Malignant: 14 (78%)
  - Non-malignant: 4
- VOD day of diagnosis post HSCT:
  - Median: 13.5 (range: 1-27)
  - <day 21: 13 (72%)
  - ***≥day 21: 5 (28%)***

- **VOD incidence: 6%**
  - Total HSCTs: 312



- Less than expected
  - m/p under- reporting
    - Missing / partial data
    - Mild VOD cases could be misdiagnosed as engraftment syndrome

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

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

VOD risk factors

- Pre-transplant factors:
  - Age (<2.5 y/o): 6
  - Disease
    - Neuroblastoma: 5
    - HLH: 1
- Transplant related factors:
  - Busulfan: 13 (72%)
  - TBI: 3
- No identifiable risk factors: 2

Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
LFT[b] (ALT, AST, GLDH)	$\leqslant 2 \times$ normal	>2 and $\leqslant 5 \times$ normal	>5	
Persistent RT[b]	<3 days	3–7 days	>7 days	
Bilirubin (mg/dL)[b, c]	<2		$\geqslant 2$	
Bilirubin (μmol/L)	<34		$\geqslant 34$	
Ascites[b]	Minimal	Moderate	Necessity for paracentesis (external drainage)	
Bilirubin kinetics				Doubling within 48 h
Coagulation	Normal	Normal	Impaired coagulation	Impaired coagulation with need for replacement of coagulation factors
Renal function GFR (mL/min)	89–60	59–30	29–15	<15 (renal failure)
Pulmonary function (oxygen requirement)	<2 L/min	>2 L/min	Invasive pulmonary ventilation (including CPAP)	
CNS	Normal	Normal	Normal	New onset cognitive impairment

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CNS = central nervous system; CPAP = continuous positive airway pressure; CTCAE = Common Terminology Criteria for Adverse Events; GFR = glomerular filtration rate; GLDH = glutamate dehydrogenase; LFT = liver function test; MOD/MOF = multi-organ dysfunction/multi-organ failure; RT = refractory thrombocytopenia; SOS/VOD, sinusoidal obstruction syndrome/veno-occlusive disease. [a]If patient fulfills criteria in different categories they must be classified in the most severe category. In addition, the kinetics of the evolution of cumulative symptoms within 48 h predicts severe disease. [b]Presence of $\geqslant 2$ of these criteria qualifies for an upgrade to CTCAE level 4 (very severe SOS/VOD). [c]Excluding pre-existent hyperbilirubinemia due to primary disease.

Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
LFT[b] (ALT, AST, GLDH)	$\leqslant 2 \times$ normal	>2 and $\leqslant 5 \times$ normal		>5

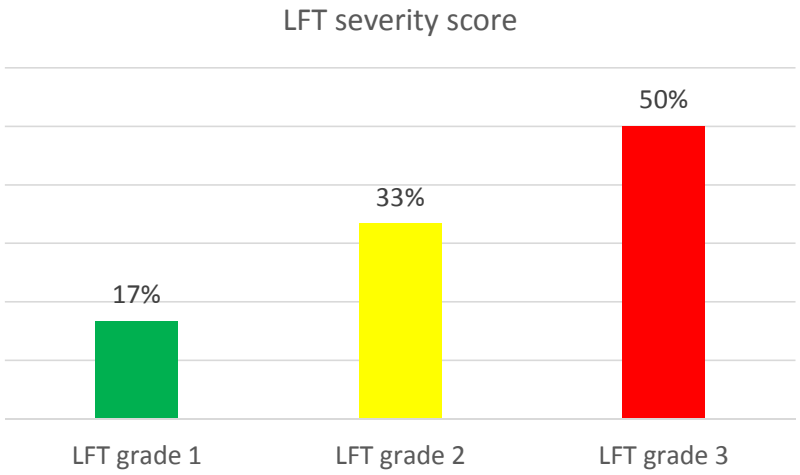
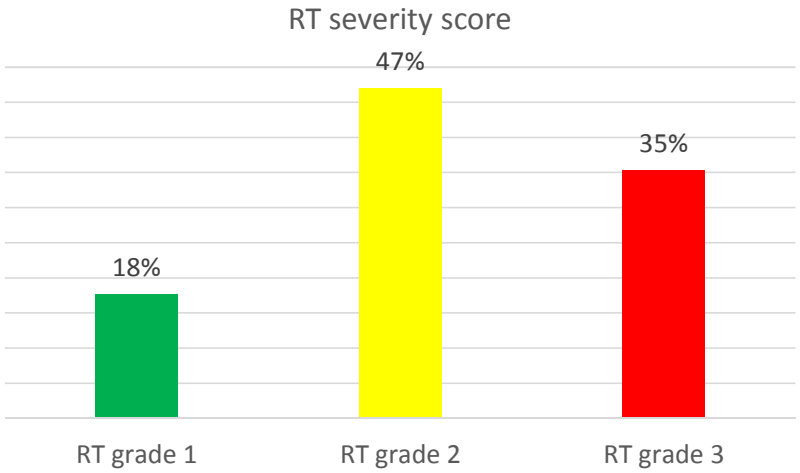


Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
Persistent RT[b]	< 3 days	3–7 days		> 7 days



RT: 16/17 (94%)

Day of RT relative to VOD Dx, median: day -1 (range: -4 to 2)

Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
Bilirubin (mg/dL)[b, c]		< 2		⩾ 2

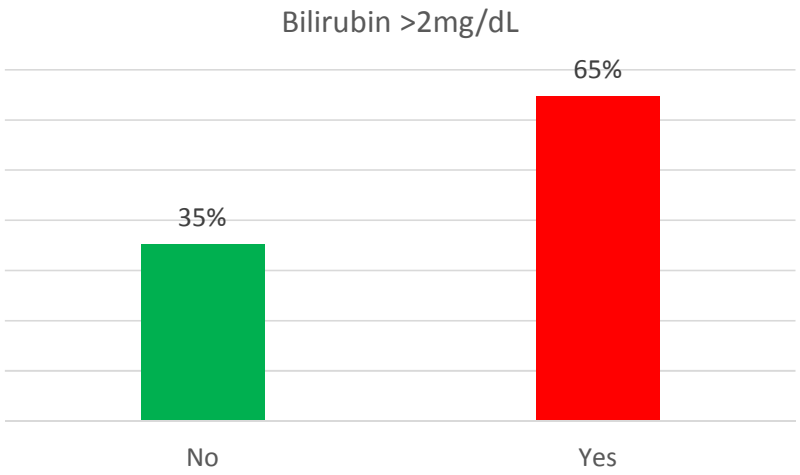


Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
Ascites[b]	Minimal	Moderate	Necessity for paracentesis (external drainage)	

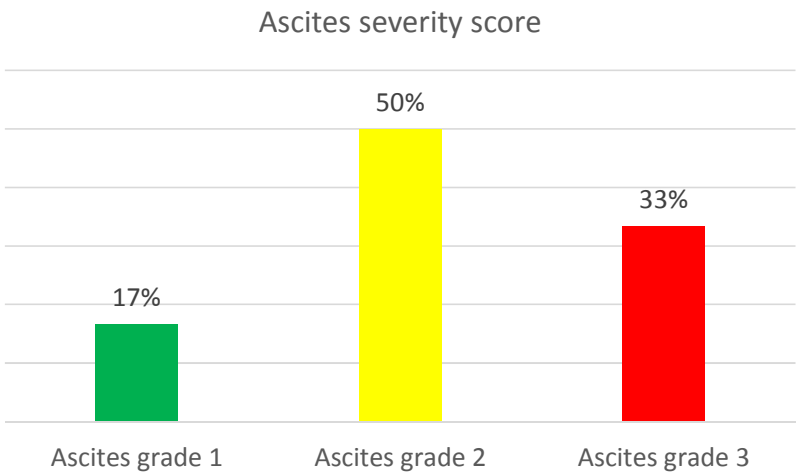
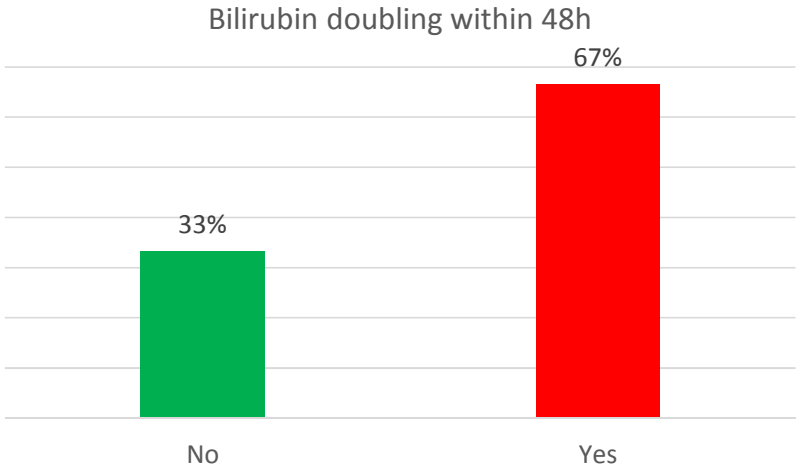


Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
Bilirubin kinetics			Doubling within 48 h	



↑ Including 1 of the lethal MOF cases

Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
Coagulation	Normal Normal		Impaired coagulation	Impaired coagulation with need for replacement of coagulation factors

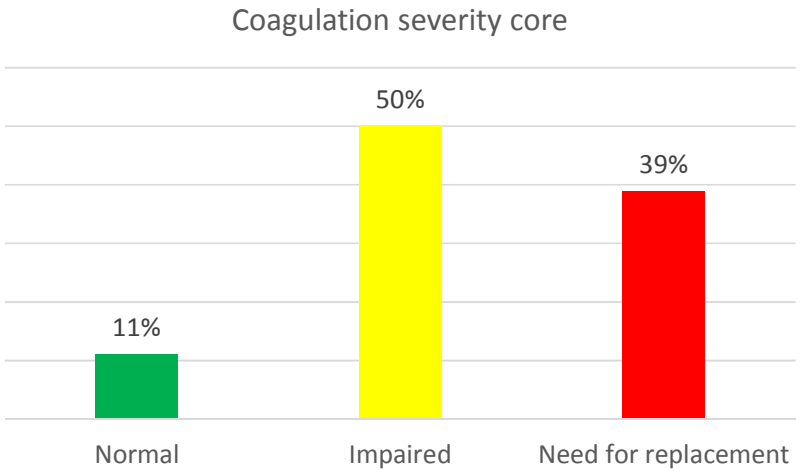
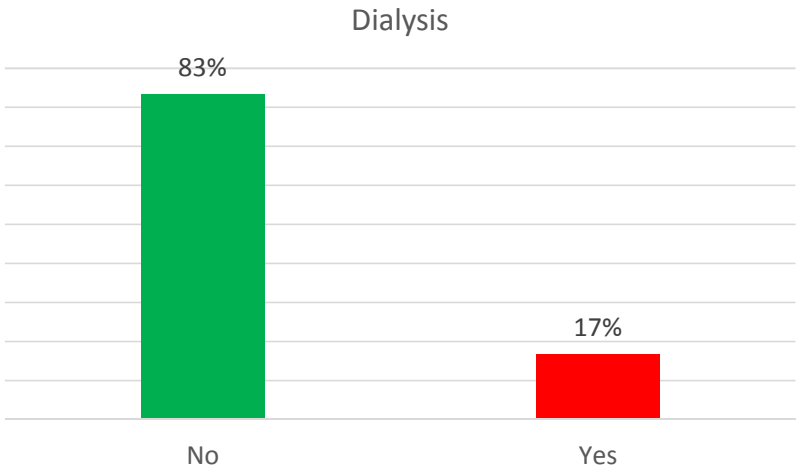


Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
Renal function GFR (mL/min)	89–60	59–30	29–15	< 15 (renal failure)



- Need for RRT: 3 (17%)
  - Renal failure: 1 (6%)
  - Encephalopathy: 2 (11%)

Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
Pulmonary function (oxygen requirement)	< 2 L/min	> 2 L/min	Invasive pulmonary ventilation (including CPAP)	

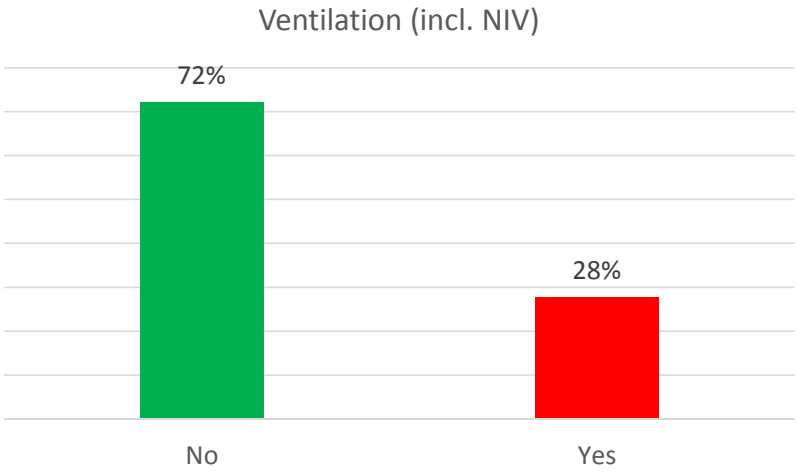
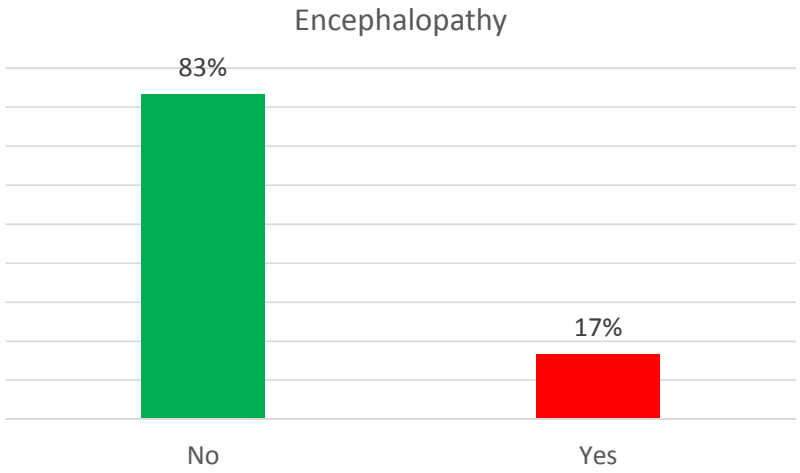


Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*



CNS	Normal	Normal	Normal	New onset cognitive impairment

VOD course:

- VOD treatment
  - Steroids: 18 (100%)
  - Defibrotide (DF): 14 (78%)
    - Day of DF start, median: day 0 (range: 0-6)
    - Length of DF Tx, median: 11 days (range: 5-21)
      - One case of DF prophylaxis
  - Paracentesis: 6 (33%)
  - Dialysis: 3 (17%)
- ICU:
  - ICU admissions: 7 (41%)
  - ICU admission post VOD Dx: 1.5 days (range: 0-10)

Bone Marrow Transplantation (2008) 41, 287–291
© 2008 Nature Publishing Group All rights reserved 0268-3369/08 $30.00
www.nature.com/bmt

ORIGINAL ARTICLE

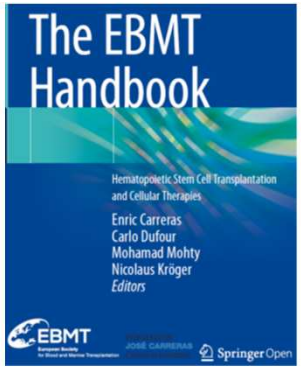
Successful treatment of hepatic veno-occlusive disease after myeloablative allogeneic hematopoietic stem cell transplantation by early administration of a short course of methylprednisolone

High-Dose Methylprednisolone for Veno-Occlusive Disease of the Liver in Pediatric Hematopoietic Stem Cell Transplantation Recipients

Biol Blood Marrow Transplant 24 (2018) 91–95
ELSEVIER
Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org

Pediatric

Combination of High-Dose Methylprednisolone and Defibrotide for Veno-Occlusive Disease in Pediatric Hematopoietic Stem Cell Transplant Recipients



E. Carreras et al. (eds.), *The EBMT Handbook*, https://doi.org/10.1007/978-3-030-02278-5_49

49.2.11 Treatment (Degree of Recommendation)
(Dignan et al. 2013; Carreras 2015)

Methylprednisolone (2C): Used by some authors. Recommended doses not defined (and range from high to low) and results difficult to analyze. Main risk: to delay treatment with defibrotide, the only agent with proved effectiveness.

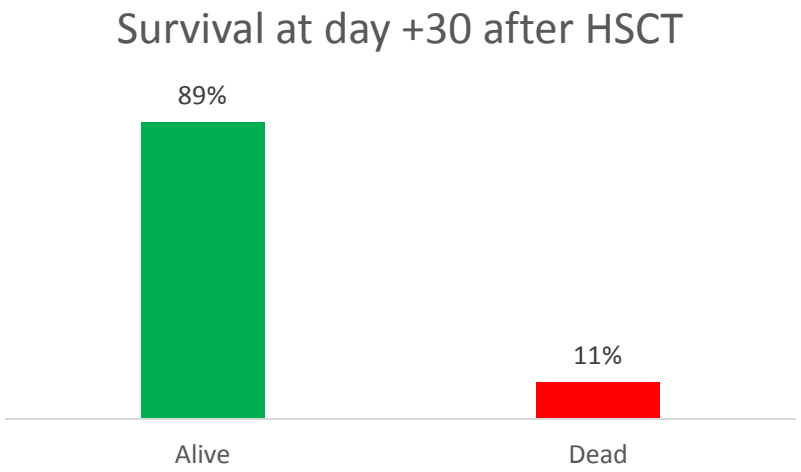
Defibrotide (1B): Despite the absence of randomized studies, it is the only agent approved by FDA and EMA to treat *severe SOS* (>80% mortality). In these patients: 50% of complete remission and > 50% SRV at day +100. Early treatment

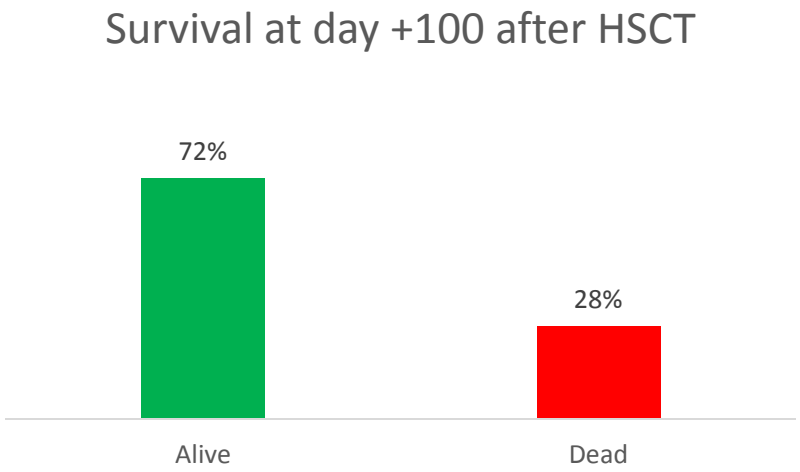
Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial

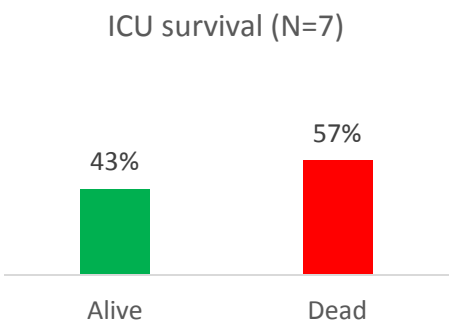
Selim Corbacioglu, Simone Cesaro, Maura Faraci, Dominique Valteau-Couanet, Bernd Gruhn, Attilio Rovelli, Jaap J Boelens, Annette Hewitt, Johanna Schrum, Ansgar S Schulz, Ingo Müller, Jerry Stein, Robert Wynn, Johann Greil, Karl-Walter Sykora, Susanne Matthes-Martin, Monika Führer, Anne O'Meara, Jacek Toporski, Petr Sedlacek, Paul G Schlegel, Karoline Ehlert, Anders Fasth, Jacek Winiarski, Johan Arvidson, Christine Mauz-Korholz, Hulya Ozsahin, Andre Schrauder, Peter Bader, Joseph Massaro, Ralph D'Agostino, Margaret Hoyle, Massimo Iacobelli, Klaus-Michael Debatin, Christina Peters*, Giorgio Dini*

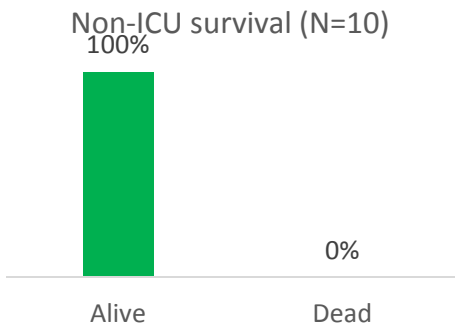
Summary
Background Hepatic veno-occlusive disease is a leading cause of morbidity and mortality after haemopoietic stem-cell Lancet 2012; 379: 1301–09

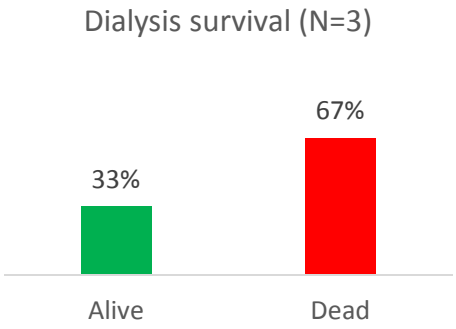
Post VOD survival:

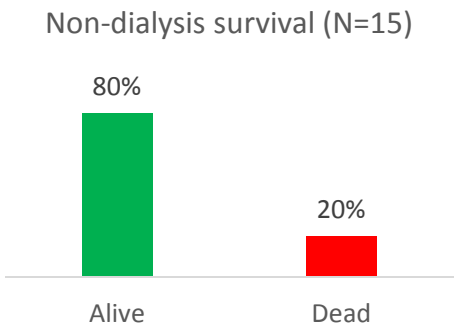












Incidence

- AKI is a common comorbidity in pediatric patients following HCT, incidence ranging from 11% to 84%.
- 5%-10% of patients may require RRT*
- Overall survival of children after HCT decreases significantly with increasing severity in AKI within the first 100 days post-HCT.
- SOS is a potentially life-threatening, early post-HCT complication.
- SOS associated with MOF has very high mortality rates, exceeding 80% despite aggressive supportive therapy**

*Pediatr Transplant. 2017 Jun;21(4). **Hematopoietic stem cell transplantation and acute kidney injury in children: A comprehensive review.** Raina R, et al.

Pediatr Transplant. 2018 Mar;22(2). **The role of continuous renal replacement therapy in the management of acute kidney injury associated with sinusoidal obstruction syndrome following hematopoietic cell transplantation. Raina R et al.

.Raina R, et al, Pediatr Transplant. June 2017
Hematopoietic stem cell transplantation and
:acute kidney injury in children
..A comprehensive review

TABLE 1 AKI risk factors. Risk factors that may lead to increased risk of AKI in both pediatric and adult patients. Studies have shown that hyperbilirubinemia, VOD, spironolactone use and septicemia correlate significantly with incidence of AKI. History of previous AKI and/or reduced renal sufficiency beforehand are also risk factors for AKI

Risk factors
Allogeneic BMT, transplantation with a non-HLA identical related or matched unrelated donor[8]
Use of drugs such as
Cyclophosphamide
Etoposide
Amphotericin B[91]
Aminoglycosides[91]
Spironolactone
Tacrolimus and Cyclosporine >200 μg/L[6]
Septicemia
Hyperbilirubinemia
Veno-occlusive disease
Grade III-IV GVHD[91]
Thrombomicroangiopathy
Total body irradiation
Increased serum creatinine pre-BMT[8]
Hypovolemia via skin or gut due to GVHD
Prior history of AKI
Reduced initial GFR
Lesions due to GVHD[91]
Foscarnet

Treatment of AKI in VOD/SOS

- Management of fluid balance is critical in the HCT patient.
- Sodium and fluid restriction
- Diuretic use
- CRRT

Criteria for CRRT initiation

- VOD/SOS with encephalopathy/hyperamonemia
- AKI- with fluid overload
- Diuretic-resistant
- Fluid overload >10%

CRRT protocol

- CRRT blood flow rates ranged from 4 to 5 mL/kg/min.
- Fluid removal rates are determined by the PICU and Nephrology physicians and adjusted as tolerated, ranging from 1 to 4 mL/kg/h.
- Heparin anticoagulation was used, dose range: 20-40units/kg/hr with ACT values of 180-220 sec.
- Replacement fluid calculated as follows: (2000 mL/h × BSA)/(1.73 m^2).
- In patients receiving defibrotide, efforts were made to keep INR <1.5 and platelets >30,000/mm^3.

Case study

- A 15-year-old female with recurrent Pre-B ALL underwent HCT, and was diagnosed with VOD 8 days after transplantation.
- Criteria for VOD: hyperbilirubinemia, enlarged liver, fluid overload - refractory to albumin and furosemide treatment. There was no neurologic compromise, blood ammonium was within normal range
- Abdominal sonography revealed ascites, enlargement of 3 hepatic veins with pulsatile flow, and enlargement of the spleen, all compatible with VOD
- Defibrotide and steroids were administered.
- Patient's course was complicated by stage IV AKI, and diuretic-resistant fluid overload.
- She suffered from line sepsis due to resistant Klebsiella pneumonia, managed with meropenem. Sepsis presented with hypotension and oliguria, further complicating the diagnosis and management of VOD.

Case study (cont.)

- Patient was transferred to the PICU and started on CRRT when reaching 6.5% FO, as she was resistant to diuretic treatment and extremely oliguric.
- 3 sessions of long (4 hours) intermittent hemodialysis were performed for 3 consecutive days, with a net ultrafiltration of 4 liters (total UF for all 3 sessions). She was hemodynamically stable with no need for catecholamine support.
- Due to coagulopathy, hemodialysis was performed with absolutely no anticoagulation (FX8 filter with high volume tubing).
- Cyclosporine treatment was converted to MMF due to its lower nephrotoxicity.
- Risk factors: Tumor lysis syndrome at presentation, necessitating a single hemodialysis session. Sepsis preceding VOD, nephrotoxins.

Case study (cont.): Outcome

- On the third day of RRT, urinary output improved, and euvolemia was achieved.
- There was no need for further diuretics or RRT treatment, since GFR and urinary output gradually improved.
- Currently, she is 1 year post VOD, suffering from CKD grade IV, reduced GFR, with no hypertension or proteinuria.

Conclusions

- Goldstein *et al*. reported that a higher degree of FO prior to CRRT initiation is independently associated with greater mortality.

  Survivors had 16% FO at CRRT initiation, as compared with 34% in nonsurvivors.

Pediatr Nephrol.95-19:91;2004. Fluid overload and acute renal failure in pediatric stem cell transplant patients. Goldstein et al.

- **Early initiation of diuretics in HCT (FO > 5%) and or CRRT (FO > 10%) prevents worsening of FO and may improve the survival (42%) of HCT patients with AKI.**

Additional important points during CRRT:

- Close monitoring of TPN, electrolytes and hydration fluids composition and rate.
- Appropriate adjustment of medication dosing.
- Daily protein intake of ~3 mg/kg/day.
- Prevention of hypothermia.

The Rambam experience

- 17 VOD patients
- 3/17 needed RRT
  - Indications for RRT: renal failure -1, encephalopathy - 2
- RRT mode CVVHDF in 1, HD in 2
- Outcome:
- 1/3 survived

Acknowledgments

Patients & families

Nurses, physicians & staff

Ruth

Ruth Rappaport Children's Hospital

Rambam Health Care Campus