Sinusoidal obstruction syndrome

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ABSTRACT

Objectives: To provide an updated version of the Sociedade Brasileira de Terapia Celular e Transplante de Medula Óssea (SBTMO) 2021 consensus on sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD), incorporating recent evidence regarding pathophysiology, risk stratification, diagnosis, prophylaxis, and treatment following hematopoietic stem cell transplantation (HSCT). **Methods:** A narrative review of the literature was performed, emphasizing studies and international recommendations published since the 2021 SBTMO consensus. Evidence regarding risk factors, diagnostic criteria, severity classification, biomarkers, imaging modalities, prophylactic strategies, and therapeutic interventions was critically reviewed, with particular focus on the refined European Society for Blood and Marrow Transplantation (EBMT) 2023 diagnostic and severity criteria. **Results:** Recent evidence supports earlier recognition of SOS through the refined EBMT 2023 criteria, which incorporate probable, clinical, and proven disease categories, dynamic bilirubin assessment, and markers of organ dysfunction, including Sequential Organ Failure Assessment-based severity evaluation. Emerging diagnostic tools, such as liver stiffness measurement and endothelial biomarkers, may improve early detection and risk stratification. Contemporary studies reinforce the benefit of prophylactic ursodeoxycholic acid and defibrotide in selected high-risk patients. Defibrotide remains the standard treatment for moderate to severe SOS, with accumulating real-world evidence demonstrating improved survival when therapy is initiated promptly after diagnosis. **Conclusions:** This updated SBTMO consensus reflects important advances in the diagnosis and management of SOS after HSCT. The integration of refined EBMT diagnostic criteria, emerging biomarkers, novel imaging techniques, and contemporary evidence on prophylaxis and treatment provides a practical framework for earlier diagnosis, improved risk stratification, timely therapeutic intervention, and potentially better clinical outcomes in this life-threatening transplant-related complication.

Keywords: Sinusoidal obstruction syndrome; Hematopoietic stem cell transplantation; Defibrotide; Endothelial injury; EBMT criteria; Hepatic complications; Transplant-related toxicity.

INTRODUCTION

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially fatal complication that occurs mainly after myeloablative conditioning (MAC) hematopoietic stem cell transplantation (HSCT), but may occur rarely after reduced-intensity conditioning (RIC), autologous HSCT, and exposure to hepatotoxic chemotherapy outside the context of transplantation, or after liver transplantation. It was initially described in patients who ingested marijuana tea containing pyrrolizidine alkaloids and was first described in 1979.[1]

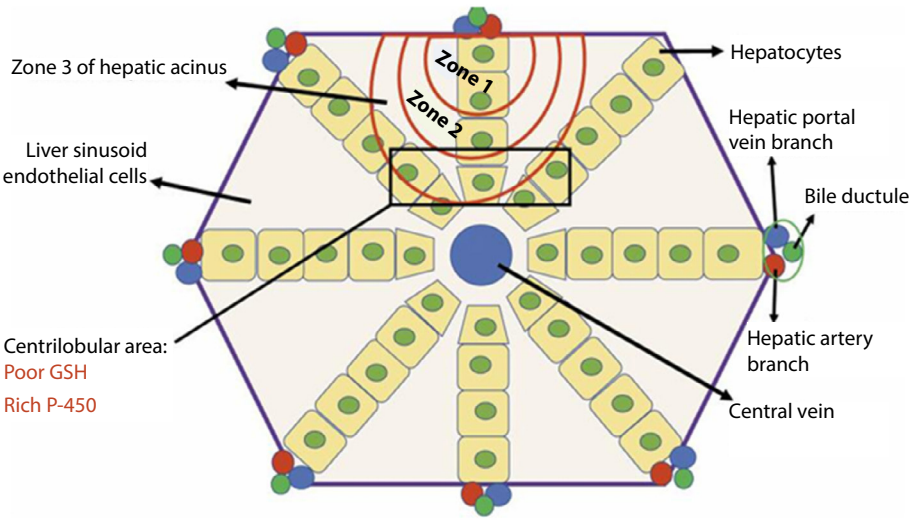
It is a disease related to hepatic vascular injury, characterized by damage to small vessels, mainly affecting the sinusoidal endothelium, which results in complications such as intrahepatic congestion, liver damage, and portal hypertension. SOS was previously called hepatic VOD until several studies suggested that injury to the hepatic sinus endothelium was greater than that to the hepatic veins.[2]

It is characterized clinically by painful hepatomegaly, weight gain, and jaundice, although anicteric forms may occur, most commonly in the pediatric population. It may evolve to multiple organ dysfunction (MOD) (with mortality exceeding 80%), pulmonary disorders (pleural effusion, pulmonary infiltrates, and hypoxia), renal failure, and/or neurological deterioration (confusion and encephalopathy). The incidence is approximately 5 to 13%, even more common in the pediatric group,[3] in which it can reach 20-30% or up to 60%. It occurs in approximately 10-15% of allogeneic HSCT with MAC conditioning and less than 5% of autologous HSCT or RIC conditioning.[4]

Pathophysiology

The basic structural component of the liver is the hepatocytes, which correspond to 80% of the organ volume and are distributed in liver slides with various functions. Through the hepatocytes flow the biliferous canaliculi, which join distally, forming increasingly larger ducts, resulting in the hepatic ducts. Among the hepatocytes, the hepatic sinusoids pass, which are fenestrated blood capillaries that receive oxygenated blood from the hepatic artery and nutrient-rich blood from the hepatic portal vein. The normal flow in the portal vein is hepatopetal, that is, directed to the liver. [1]

Between the sinusoids and hepatocytes, we have the space of Disse, where the microvilli of the hepatocytes extend. Hepatic sinusoids are coated by endothelial cells, whose function is filtration and removal of metabolites (Fig. 1).[5]



Source: Nassereddine et al.[5]

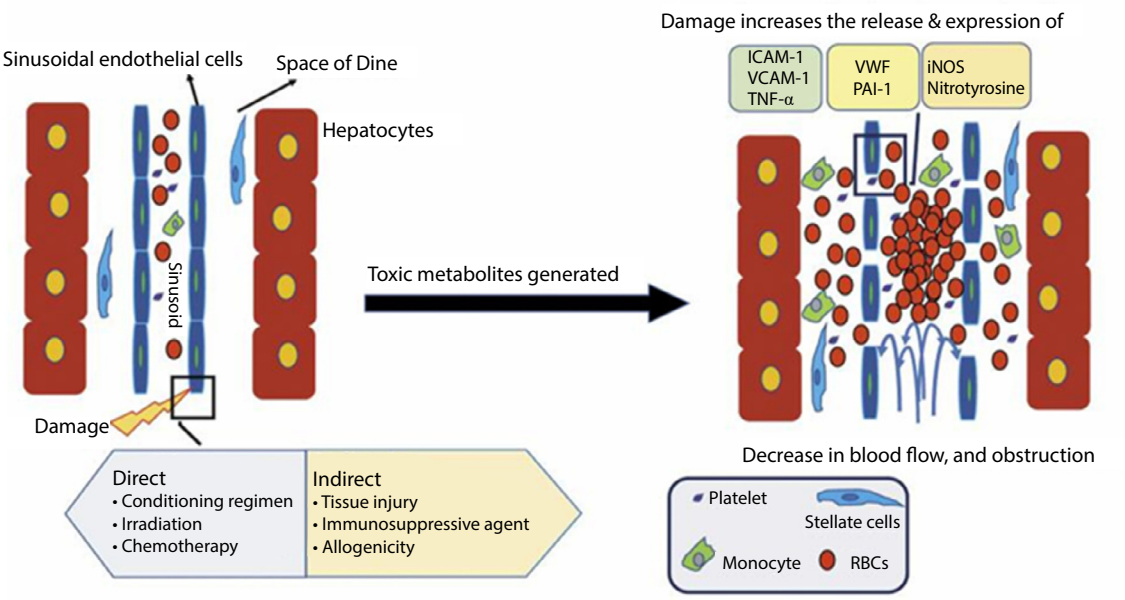
Figure 1. Hepatic acinus. Obstruction of the hepatic sinusoids mainly occurs in zone 3 of the hepatic acinus. The centrilobular area of zone 3 has a low concentration of glutathione (GSH), which is important for protecting hepatic cells from toxic metabolites by converting them into non-toxic metabolites.

The initial event in SOS is endothelial injury of the hepatic sinusoid, with loss of cohesion between the endothelial cells, extravasation of red blood cells (RBCs) into the space of Disse, with embolization through the centrolobular vein and subsequent post-sinusoidal obstruction.[1]

The etiologies of endothelial injury are conditioning regimens (mainly busulfan and cyclophosphamide metabolites), cytokines produced by injured tissues, microbial products resulting from the breaking of the mucosal barrier, drugs used during transplantation (such as granulocyte colony-stimulating factors or calcineurin inhibitors), the grafting process, and allo-reactivity.[1]

Chemotherapeutic drugs are metabolized by cytochrome P450, producing toxic metabolites that are converted by the glutathione enzymatic system into non-toxic metabolites to later be eliminated. The centrolobular regions of the liver are poor in glutathione and for this reason are more sensitive to the action of toxic agents. The immaturity of this enzymatic system in the pediatric group may explain the higher incidence of SOS in children. The higher incidence after allogeneic HSCT and in unrelated transplants suggests the participation of alloreactivity in the pathophysiology of SOS. Activated sinus endothelial cells increase the production of cytokines, heparinase, and the expression of adhesion molecules, with loss of cytoskeletal structure, space formation that facilitates the extravasation of RBCs, leukocytes, and cellular debris into the space of Disse, with narrowing of the sinusoids.[1]

The increase in tissue factor and plasminogen activator inhibitor-1 (PAI-1) leads to a procoagulant and hypofibrinolytic state, with consequent fibrin clot formation, narrowing and obstruction of the hepatic sinusoid (Fig. 2).[5]



Source: Nassereddine et al.[5]

Figure 2. SOS pathogenesis. Left: normal blood flow with intact sinusoidal endothelial cells. Right: sinusoidal endothelial cells damaged by direct and indirect factors. The damage promotes the appearance of gaps in the sinusoidal barrier. RBCs, platelets, and monocytes penetrate the space of Disse due to an increase in the release and expression of cytokine molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), tumor necrosis factor-alpha (TNF-α), von Willebrand factor (VWF), PAI-1, and inducible nitric oxide synthase (iNOS). The endothelial lining consequently detaches. The result is a decrease in blood flow and obstruction that will lead to embolization and post-sinusoidal hypertension.

Detachment of endothelial cells is correlated with nitric oxide deficiency caused by post-conditioning toxicity. Nitric oxide deficiency promotes increased production of matrix nine, responsible for the detachment of endothelial cells. Obstruction of blood flow is promoted by the proliferation of perisinusoidal star cells and subendothelial fibroblasts in the terminal hepatic vein, followed by the deposition of the extracellular matrix. Then fibrosis extends to the liver parenchyma, leading to blockage of the blood output from the liver, leading to hepatic congestion and development of post-sinusoidal portal hypertension.[3]

METHODS

Risk factors

The analysis of risk factors with the identification of subgroups of patients at higher risk for developing severe forms of the disease is necessary for early intervention and to prevent the development of MOD.[4,6]

There are three risk factors: related to transplantation; related to the patient or underlying disease; and liver-related factors.

- HSCT-related factors
- Allogeneic HSCT is at higher risk when compared to autologous HSCT
- Unrelated donor
- Donor with mismatch
- Non-T-cell-depleted transplant
- MAC
- Conditioning regimen with high doses of busulfan or oral formulation; melphalan; cyclophosphamide
- High doses of total body irradiation (TBI)
- Second myeloablative transplant
- Interval between diagnosis and HSCT > 13 months
- Pharmacological prophylaxis of graft-versus-host disease (GVHD): association of sirolimus, methotrexate and tacrolimus; cyclosporine and methotrexate.

Factors related to the patient or the disease

- Low age in children and advanced age in adults
- Hepatitis B/C-positive serology
- Positive serology for cytomegalovirus
- Low Karnofsky index (< 90%)
- Metabolic syndrome
- Active disease at HSCT
- High ferritin levels
- Women on hormonal contraceptives
- Use of parenteral nutrition up to 30 days before HSCT
- Thalassemia, advanced malignancy, acute leukemia, acute Chediak-Higashi syndrome, late platelet grafting
- Genetic factors (GSTM1 polymorphism, C282Y hemochromatosis mutations, MTHFR 677CC/1298CC haplotype)

Liver-related factors

- Transaminases above 2.5 times the upper limit of normal
- Bilirubin level above 1.5 times the upper limit of normal
- Low albumin level

- Active viral hepatitis
- Cirrhosis
- Liver or abdominal irradiation
- Iron overload (high serum ferritin levels)
- Previous use of gentuzumab ozogamicin[7]
- Hepatotoxic drugs

Pediatric risk factors

- Hemophagocytic lymphohistiocytosis
- Adrenoleukodystrophy
- Osteopetrosis
- Neuroblastoma with high doses of chemotherapy
- Age (< 1–2 years)
- Low weight
- Chronic myelomonocytic leukemia
- Juvenile myelomonocytic leukemia
- Hemoglobinopathies

Risk score for SOS development after allogeneic HSCT

A risk score for the development of SOS may be useful in identifying high-risk patients to seek preventive strategies for this complication, which can be fatal. The Center for International Blood and Marrow Transplant Research developed a pre-transplant risk score through the evaluation of 13,097 patients submitted to the first allogeneic HSCT from 2008 to 2013, and prognostic factors for the development of SOS up to D+100 after transplantation were identified through analysis with a multivariate logistic regression model. Variables with significance in the risk score:

- Age (children > adults)
- Performance score (Karnofsky) < 90%
- Use of sirolimus
- Hepatitis B/C (positive hepatitis B and C or only positive hepatitis B)
- Conditioning regimen (MAC regimen with melphalan, fludarabine, busulfan with serum level monitoring; TBI)
- Status pre-HSCT/underlying disease (bone marrow aplasia, Hodgkin and non-Hodgkin lymphoma, myelodysplastic syndrome, advanced chronic myeloid leukemia, and myeloproliferative syndromes).

The model can be brought into clinical practice with an online risk calculator, accessible to the public via the link: https://cibmtr.org/CIBMTR/Resources/Research-Tools-Calculators/VOD-Risk-Calculator

With the use of the tool, patients at elevated risk for developing SOS may have closer follow-up, and modifications in the conditioning regimen may be discussed. The identification of high-risk patients may also facilitate the early initiation of drug therapy with defibrotide from the first symptoms of SOS, which demonstrated improvement in the survival of patients who developed this complication.[8]

Clinical manifestations

They are due to portal hypertension and usually occur during the first 21 days of HSCT but may occur later in 15 to 20% of cases (21-508 days). It can range from mild clinical manifestations with spontaneous resolution in a few weeks to MOD, with high mortality. Given the severity of the condition, daily monitoring of weight, abdominal circumference, diuresis, and water balance is necessary for early diagnosis of the complication.[3,4]

The characteristic clinical manifestations are weight gain, generally not responsive to diuretics, hyperbilirubinemia, painful hepatomegaly, and ascites.

The diagnosis of SOS was classically based on the clinical criteria of modified Baltimore[9] or Seattle,[10] the 2016 EBMT criteria, and the exclusion of differential diagnoses (Table 1). The refined EBMT criteria introduced in 2023 represent an important conceptual shift in the diagnosis of SOS after HSCT. One of the key innovations of this framework is the introduction of diagnostic categories that allow recognition of the syndrome before classical features become fully established.

Table 1. SOS diagnostic criteria in adults.

Modified Seattle Criteria	Baltimore Criteria	EBMT Criteria 2016
Presence in the first 21 days of HSCT of two or more criteria: Bilirubin > 2 mg/dL; painful hepatomegaly Weight gain > 2% of baseline	Presence within the first 21 days of HSCT Bilirubin > 2 mg/dL and at least two of the following: Painful hepatomegaly Weight gain >5% Ascites	Classic SOS Presence within the first 21 days of HSCT: Bilirubin > 2 mg/dL and at least two of the following Weight gain > 5% Ascites Painful hepatomegaly Late SOS Classic SOS after 21 days or histological diagnosis or two or more criteria below (and evidence with US) Bilirubin > 2 mg/dL Painful hepatomegaly Weight gain > 5% Ascites

Presence of two or more parameters: unexplained refractoriness to platelet transfusion; weight gain for 3 consecutive days even with diuretic use or weight gain > 5% of basal weight; hepatomegaly (best if confirmed by imaging such as US, computed tomography (CT), or MRI; ascites (best if confirmed by imaging such as US, CT, or MRI); bilirubin rising above baseline for 3 consecutive days or increase > 2 mg/dL in 72 h. Source: Elaborated by the authors.

Rather than relying exclusively on fixed thresholds such as hyperbilirubinemia, the refined criteria recognize the dynamic nature of the disease and emphasize early clinical changes, including unexplained weight gain, hepatomegaly, ascites, and progressive bilirubin elevation. Importantly, the new framework allows clinicians to classify cases as probable, clinical, or proven SOS depending on the level of diagnostic certainty.[11]

The refined EBMT diagnostic framework for SOS incorporates progressive diagnostic categories that allow earlier recognition of the syndrome. As shown in Table 2, the classification distinguishes between probable, clinical, and proven SOS based on the combination of clinical findings, laboratory abnormalities, and confirmatory evidence, when available.[11]

Table 2. SOS diagnostic criteria in adults according to the refined EBMT classification 2023.

	Probable SOS	Clinical SOS	Proven SOS
Diagnostic criteria	Two of the following criteria must be present: -Bilirubin ≥ 2 mg/dL -Painful hepatomegaly -Weight gain > 5% -Ascites -US and/or elastography suggestive of SOS	Bilirubin ≥ 2 mg/dL and two of the following criteria must be present: -Painful hepatomegaly -Weight gain > 5% - Ascites	Histologically proven SOS or hemodynamically proven disease (HVPG ≥ 10 mmHg)
Onset	In the first 21 days after HSCT: classical SOS after day +21: late-onset SOS		
Exclusion criteria	Clinical findings should not be attributable to alternative diagnoses		

HVPG: hepatic venous pressure gradient. Source: Elaborated by the authors.

Importantly, the refined criteria acknowledge that SOS may present both during the classical early period within the first 21 days after HSCT and as late-onset disease occurring beyond day +21. Furthermore, the diagnostic framework emphasizes that these findings must not be attributable to alternative causes such as GVHD, sepsis, drug-induced liver injury, or other hepatic complications following transplantation.[11]

This structured approach allows clinicians to recognize evolving clinical phenotypes earlier than with previous diagnostic definitions and may therefore facilitate earlier therapeutic intervention (Table 3).

Table 3. Comparison of EBMT 2016 vs. refined EBMT 2023 criteria.

Feature	EBMT 2016	Refined EBMT 2023
Diagnostic framework	Fixed clinical criteria	Probable/Clinical/Proven categories
Bilirubin requirement	Often required	Not mandatory in early diagnosis
Early diagnosis	Limited	Expanded recognition of early disease
Organ dysfunction	Considered	Integrated into severity scoring
SOFA score	Not included	Included in severity assessment

Source: Elaborated by the authors.

In addition to refining diagnostic categories, the EBMT group proposed an updated severity classification that integrates markers of organ dysfunction. These include renal impairment, respiratory compromise, and the presence of multiorgan failure, as well as dynamic assessment of bilirubin kinetics. The inclusion of elements derived from the Sequential Organ Failure Assessment (SOFA) score allows clinicians to evaluate disease severity and prognosis more accurately (Table 4).

Table 4. SOFA score.

Organ system	0	1	2	3	4
Respiratory (PaO2/FiO2)	> 400	≤ 400	≤ 300	≤ 200	≤ 100
Coagulation (platelets × 10^9/L)	≥ 150	< 150	<1 00	< 50	< 20
Liver (bilirubin mg/dL)	< 1.2	1.2-1.9	2-5.9	6-11.9	≥ 12
Cardiovascular	Normal	MAP < 70	Vasopressor low dose	Vasopressor moderate dose	Vasopressor high dose
Central nervous system (Glasgow Coma Scale)	15	13-14	10-12	6-9	< 6
Renal (creatinine mg/dL)	< 1.2	1.2-1.9	2-3.4	3.5-4.9	≥ 5

Source: Elaborated by the authors.

Progressive increases in the SOFA score indicate worsening organ dysfunction and may support the classification of severe or very severe SOS. This multidimensional approach reflects the understanding that SOS is a systemic endothelial disorder rather than a purely hepatic condition.

RESULTS

Validation of the refined EBMT criteria

Since publication of the refined EBMT criteria, several studies have evaluated their performance in clinical practice (Table 5). Early analyses using EBMT registry data demonstrated that application of the refined criteria allows earlier recognition of SOS compared with previous definitions.

Table 5. Studies evaluating the refined EBMT diagnostic criteria.

Study	Year	Study design	Population	Main findings
Mohty et al.[4,11]	2023	Consensus and validation analysis	EBMT registry	Introduction of refined diagnostic and severity criteria
Yoon et al.[13]	2025	Real-world observational cohort	Adults with SOS	Early diagnosis associated with improved outcomes with defibrotide

Source: Elaborated by the authors.

In these analyses, a substantial proportion of patients met diagnostic criteria before fulfilling the classical Baltimore or EBMT-2016 thresholds. Earlier recognition was particularly relevant in patients with rapidly progressive disease, where timely initiation of therapy may significantly influence outcomes.

Subsequent observational studies further confirmed the clinical value of the refined criteria. In retrospective cohorts of adult HSCT recipients, investigators found that the updated severity classification correlated strongly with survival outcomes, particularly day-100 mortality following transplantation. Patients classified as having severe or very severe SOS according to the refined EBMT framework demonstrated significantly poorer survival compared with those with mild or moderate disease.[12]

These findings support the prognostic validity of the refined classification system and suggest that it may improve risk stratification and therapeutic decision-making.

Importantly, several real-world studies have also demonstrated that earlier diagnosis enabled by the refined criteria may facilitate earlier initiation of defibrotide therapy.[13] Given the strong association between treatment timing and survival outcomes, this represents a clinically meaningful advantage.

Differential diagnosis

- Volume overload
- Constrictive pericarditis
- Drugs causing liver injury and cholestasis
- Sepsis
- Infectious hepatitis
- Parenteral nutrition and biliary complications
- Cholestasis
- GVHD

Severity degrees

According to EBMT criteria (Table 6).

Table 6. Severity degrees.

Adults[4]				
	Mild	**Moderate**	**Severe**	**Very severe**
Onset of symptoms, days	7	5-7 d	< 4	Anytime
Bilirubin (mg/dL)	> 2 and < 3	> 3 and < 5	> 5 and < 8	> 8
Increase in BT			Double in 48 h	
AST/ALT	2 ×	> 2 and > 5 ×	> 5 and > 8 ×	> 8 ×
Weight gain (%)	< 5	> 5 and < 10	> 5 and < 10	>10
Creatinine (relative to baseline pre-HSCT)	< 1.2 ×	> 1.2 and < 1.5 ×	> 1.5 and < 2 ×	> 2 × or MOD
Children[10]				
AST/ALT	< 2 ×	> 2and < 5		> 5 ×
Refractoriness to platelet transfusion, days	< 3	3-7		> 7
Bilirubin (mg/dL)	< 2	< 2	< 2	> 2
Increase in BT				Double in 48 h
Ascites	Minimal	Moderate	Moderate	Paracentesis
Clotting studies	Normal	Normal	Changed	Need reset coagulation factors
Renal function (mL/min)	89-60	59-30	29-15	< 15
Lung function (O_2 need)	< 2 L/min	> 2 L/min	Vm	Vm
Central nervous system impairment	Out	Out	Out	Cognitive impairment

Source: Elaborated by the authors.

Diagnosis

The diagnosis is essentially clinical and based on the clinical criteria of modified Baltimore or Seattle, and, recently, on the refined EBMT criteria score, as previously described.

Given the high mortality of severe SOS (> 80%), daily monitoring of the patient should be performed from conditioning to at least 14 days after transplantation, especially when the patient presents risk factors; monitor for jaundice, weight gain, positive water balance, ascites, edema, and hepatomegaly, emphasizing that in the pediatric population the absence of jaundice is not uncommon.[14]

Percutaneous liver biopsy should be avoided due to the risk of bleeding; transjugular liver biopsy can minimize the risk of bleeding and enables measurement of hepatic vein pressure.

Potential proposed biomarkers: PAI-1, von Willebrand factor (VWF), thrombomodulin, soluble ICAM-1, tumorigenicity suppressor 2, angiopoietin-2, hyaluronic acid, interleukin-6, interleukin-10, and CD97.

Some studies suggest that combinations of endothelial biomarkers may allow risk stratification before the onset of clinical disease. A biomarker-based prognostic test for the assessment of SOS risk, termed "VODCheck," incorporates hyaluronan, ANG-2, and thrombomodulin, and showed prognostic accuracy.[15] However, variability between studies and lack of standardized thresholds currently limit their clinical application.

Ongoing research is exploring the integration of biomarker panels with clinical and imaging parameters to develop predictive models for early SOS detection.

Ultrasonography: many studies report the importance of the test to exclude other diagnoses. Some findings that may be present are hepatomegaly, splenomegaly, vesicle wall thickening (> 6 mm), enlargement of portal vein diameter > 8 mm in children and 12 mm in adults, hepatic vein diameter < 3 mm, ascites, and visualization of the paraumbilical vein.[16]

Doppler ultrasound (US): approximately 83% sensitivity and 87% specificity in the presence of the following criteria:

- Flow modulation in the portal vein
- Decrease in density and spectrum
- Hepatofugal flow or maximum speed less than 10 cm/second
- Portal vein congestion (index:2: 0.1)
- Hepatic artery resistive (index :2: 0.75)
- Single-phase flow in the hepatic vein
- Demonstration of flow in the periumbilical vein

Magnetic resonance imaging: in recent years, imaging modalities have been investigated as potential tools for early detection of SOS. Among these, liver stiffness measurement (LSM) using transient elastography has attracted particular attention.

Prospective studies have demonstrated that increases in liver stiffness may precede the clinical diagnosis of SOS by several days. This observation suggests that elastography may detect early hemodynamic changes associated with sinusoidal obstruction before the development of overt clinical manifestations. The ELASTOVOD is the most important prospective multicenter study to date. It included screening across 25 Italian centers, with 774 adults and 167 children included in the analysis. The proposed algorithm achieved ≥ 95% sensitivity and specificity, using 6 kPa as a rule-out threshold and 25 kPa as a rule-in threshold, in addition to the "three-times pre-HSCT rule." The study also showed that LSM can help differentiate SOS from other hepatic complications up to day +100 after HSCT.[17]

Prophylaxis

- Iron chelation prior to HSCT
- Avoid use of alcohol and hepatotoxic drugs
- If possible, RIC regimen
- 2-day interval between busulfan and cyclophosphamide
- 1-day interval between busulfan and melphalan
- Pharmacokinetic study of busulfan

Avoid G-CSF: used to accelerate the recovery of neutropenia but increases the adhesion molecules (VCAM-1 and E-selectin) and can activate endothelial cells.[18]

Ursodeoxycholic acid: a randomized, double-blind, placebo-controlled study showed a lower incidence of SOS in the group that received ursodeoxycholic acid prophylaxis at a dose of 300 mg twice daily, or 900 mg in patients weighing over 90 kg.[19] It should be initiated before conditioning and maintained up to D+90 post HSCT in allogeneic or high-risk autologous HSCT.

In 2024, a network meta-analysis by Sousa-Pimenta et al.[20] confirmed the benefit of defibrotide and ursodeoxycholic acid in reducing the incidence of SOS following HSCT.

Defibrotide: until 2021, there was no robust evidence in adults; only one randomized study in the pediatric age group demonstrated a reduction in the incidence of SOS but without benefit in survival.[16]

In 2026, a meta-analysis conducted by Corbacioglu et al.[21] demonstrated that prophylactic use of defibrotide significantly reduced the risk of SOS, with a reported risk ratio of 0.30 in high-risk populations. Similarly, a network meta-analysis by Sousa-Pimenta et al.[20] confirmed the benefit of defibrotide and ursodeoxycholic acid in reducing the incidence of SOS following HSCT.

Children with risk factors: 6.25 mg/kg EV four times a day.[8] Adults: 6.25 mg/kg EV four times a day.[8]

Eicosapentaenoic acid (EPA): emerging therapeutic approaches targeting endothelial dysfunction are also under investigation. In a clinical study, Miyazaki et al.[22] evaluated the use of EPA in allo-HSCT recipients and reported a reduction in the incidence of SOS, suggesting a potential role for anti-inflammatory and endothelial-protective strategies.

Heparin: there is no robust evidence for use in adults. Systematic reviews cannot demonstrate benefits in SOS prevention or overall survival for both autologous and allogeneic HSCT, due to the great heterogeneity of randomized controlled studies, with variations in the initiation of prophylaxis and/or duration.[20,23-25]

Treatment

The treatment of SOS may include supportive and intensive care in addition to specific therapy with defibrotide. Supportive care and clinical monitoring are critical in the management of SOS throughout the HSCT.

Daily reports of various parameters such as abdominal circumference and weight are recommended to promptly capture the clinical diagnostic criteria and to record all dynamic changes and evaluate the response to treatment and disease progression.[3]

Supportive treatment

The basis of supportive treatment in patients with SOS is clinical care, particularly regarding water balance. The total amount of fluids should be restricted and diuretic therapy instituted. Renal replacement therapy may be required in severe cases. Patients with multiple organ failure will need management in an intensive care environment. Initial discussion with a specialized hepatology unit is advised regarding other therapeutic options.[19]

In addition to the use of diuretics, ultrafiltration, hemodialysis, and water restriction, oxygen support, paracentesis, and thoracentesis may also be necessary. It is also recommended to maintain hemoglobin levels around 8 g/dL and avoid transfusion of ABO-incompatible platelets.

- Defibrotide: 25 mg/kg/day divided into four daily doses for 21 days or until MOD resolution.

Defibrotide is the only drug licensed for the treatment of moderate/severe SOS. It consists of a combination of oligodeoxyribonucleotides derived from the intestinal mucosa of the pig and has antithrombotic, profibrinolytic, and anti-inflammatory properties, in addition to a protective effect on the endothelium.[16,26]

Common adverse reactions are (> 1% to < 10%): intracranial, gastrointestinal, pulmonary, epistaxis, hematuria, and bleeding at the catheter site.

The introduction of the refined EBMT diagnostic criteria in 2023 has important implications for the treatment of SOS, primarily by enabling earlier identification of patients and consequently earlier initiation of therapy. In this context, several recent studies published after 2023 have evaluated treatment outcomes in contemporary cohorts (Table 7).

Table 7. Clinical studies on SOS treatment published after 2023.

Study	Year	Study design	Population	Therapy evaluated	Key findings
Yoon et al.[13]	2026	Retrospective real-world cohort	73 adults with severe SOS	Defibrotide	Early initiation (≤ 2 days) improved 100-day survival; high bilirubin predicted worse outcomes
Ruutu et al.[12]	2023	EBMT registry analysis	Adult allo-HSCT recipients	Defibrotide	SOS resolution in 58%; day-100 survival ~57%
Gómez-Centurión et al.[27]	2024	Observational cohort	HSCT recipients	Defibrotide	Complete response ~65%
Goto et al.[28]	2024	Pediatric observational study	HSCT recipients	Early defibrotide	Improved severity and survival
Kleinschmidt et al.[29]	2025	Clinical outcome study	HSCT and non-HSCT SOS	Defibrotide	Effective across settings; acceptable safety profile
Corbacioglu et al.[21]	2026	Meta-analysis	High-risk HSCT	Defibrotide prophylaxis	Risk reduction (RR ~0.30)
Sousa-Pimenta et al.[20]	2024	Network meta-analysis	HSCT recipients	Defibrotide, UDCA prophylaxis	Reduced incidence of SOS
Miyazaki et al.[22]	2025	Clinical study	Allo-HSCT	EPA prophylaxis	Reduced SOS incidence

Source: Elaborated by the authors.

Defibrotide remains the cornerstone of therapy for moderate to severe SOS, and recent real-world data further reinforce its clinical benefit. In a retrospective cohort study including 73 adult patients with severe or very severe SOS, Yoon et al.[13] demonstrated that overall survival at day 100 was significantly higher when defibrotide was initiated within 2 days of diagnosis. Importantly, elevated bilirubin levels at the time of treatment initiation were associated with worse outcomes, supporting the concept that earlier recognition and treatment are critical determinants of prognosis.

These findings are consistent with registry-based data from EBMT. In an analysis of adult allogeneic HSCT recipients, Ruutu et al.[12] reported that defibrotide-treated patients achieved resolution of SOS in approximately 58% of cases, with a day-100 survival rate of around 57%. Although not designed specifically to evaluate the timing of therapy, this study reflects the real-world effectiveness of defibrotide in contemporary transplant practice.

Additional observational studies further support these findings. In a cohort reported by Gómez-Centurión et al.[27] complete response rates of approximately 65% were observed among patients with SOS after HSCT, with the majority receiving defibrotide therapy. Similarly, in a pediatric observational study, Goto et al.[28] demonstrated that early initiation of defibrotide was associated with improved severity grading and survival outcomes, highlighting the importance of early therapeutic intervention even in younger populations.

More recently, Kleinschmidt et al.[29] evaluated outcomes in patients with SOS in both HSCT and non-HSCT settings and confirmed that defibrotide remains effective across different clinical contexts, with an acceptable safety profile. These findings reinforce the role of defibrotide as the standard therapeutic agent in SOS.

Taken together, these studies support a treatment paradigm in which early diagnosis – facilitated by the refined EBMT criteria – enables earlier initiation of defibrotide, which in turn is associated with improved clinical outcomes. They also highlight ongoing efforts to expand therapeutic options beyond defibrotide, particularly through strategies targeting endothelial injury.

Corticosteroids

Therapy with high-dose steroids may be an option in some cases where defibrotide is not available.

Although defibrotide remains the primary disease-specific therapy, corticosteroids have historically been explored as an adjunctive treatment strategy in SOS due to their potential anti-inflammatory and endothelial-stabilizing properties.

Early observational studies suggested that high-dose corticosteroids might improve hepatic inflammation and sinusoidal endothelial injury in selected patients. In particular, pulse-dose methylprednisolone has been investigated in patients with early SOS, with some reports suggesting improvement in bilirubin levels and clinical symptoms.[23]

More recent reviews of SOS management indicate that corticosteroids may still be considered in selected clinical scenarios, particularly when inflammatory mechanisms or overlapping complications such as GVHD are suspected. However, the available evidence remains limited and largely based on small observational cohorts, and corticosteroids are not currently recommended as standard therapy in international guidelines.[30]

Nevertheless, corticosteroids may still be used in some transplant centers as part of multimodal supportive therapy, particularly in cases where defibrotide is not immediately available or when clinical uncertainty exists between SOS and other post-transplant hepatic complications.

Further prospective studies are required to determine whether corticosteroids may play a role as adjunctive therapy in early or moderate stages of the disease.

The recommended schedule consists of intravenous methylprednisolone 500 mg/m^2 per dose every 12 hours for six doses, followed by a gradual reduction to 2 mg/kg/day for 3 days, and subsequently decreased according to the preference of the attending physician.[31]

Ascitic fluid drainage with a peritoneal dialysis catheter

Use of a peritoneal dialysis catheter for intra-abdominal fluid removal in children with severe SOS, followed by intravascular fluid administration to preserve perfusion and renal function, preventing MOD.[32]

The therapeutic use of TIPS has been reported in a few case series, but it is not usually recommended due to weak evidence.[33]

CONCLUSION

Table 8 summarizes the recommendations from the 2026 SOS consensus.

Table 8. Summary of recommendations from the 2026 SOS consensus.

Category	Intervention/method	Description	Grade of recommendation	Level of evidence
Diagnosis	Biomarkers	PAI-1, VWF, thrombomodulin, soluble ICAM-1, ST2, angiopoietin-2, hyaluronic acid, IL-6, IL-10, CD97	B	Weak (2c)
Diagnosis	Ultrasonography	Hepatomegaly, splenomegaly, gallbladder wall thickening, portal vein enlargement, hepatic vein <3 mm, ascites, paraumbilical vein	B	Weak (2b)
Diagnosis	Hepatic elastography	Liver stiffness measurement, a non-invasive diagnostic tool for SOS following HSCT	A	Strong (1c)
Prophylaxis	Defibrotide (children)	6.25 mg/kg IV every 6 hours in children with risk factors	A	Strong (1a)
Prophylaxis	Defibrotide (adults)	6.25 mg/kg IV every 6 hours. Most benefit for allogeneic grafts	A	Strong (1c)
Prophylaxis	Ursodeoxycholic acid	Dose: 300 mg twice daily or 900 mg/day in patients >90 kg; should be initiated before conditioning and maintained until day +90 post-HSCT in allogeneic or high-risk autologous HSCT	A	Strong (1c)
Prophylaxis	Heparin	No strong evidence for benefit in prevention or overall survival; high heterogeneity across studies	B	Moderate (2b)
Prophylaxis	EPA (EPA)	1800 mg/d, divided into 2 or 3 doses. Only one retrospective study	B	Moderate (2b)
Treatment	Defibrotide	25 mg/kg/day divided into 4 doses for 21 days or until resolution of multiorgan dysfunction	A	Strong (1A)
Treatment	Corticosteroids	High-dose methylprednisolone: 500 mg/m^2 IV every 12 hours for 6 doses, followed by taper to 2 mg/kg/day and gradual reduction; option when defibrotide is not available	B	Weak (2C)
Treatment	Ascitic fluid drainage (peritoneal catheter)	Use in children with severe SOS to remove intra-abdominal fluid and maintain perfusion and renal function, preventing MOD	B	Weak (2D)
Treatment	TIPS	Transjugular TIPS reported in small case series	C	Weak (2D)

Source: Elaborated by the authors.

CONFLICTS OF INTEREST

Nothing to declare.

AUTHOR CONTRIBUTIONS

Conceptualization: Santos FR, Paton EJA; **Investigation:** Santos FR, Paton EJA, Salvino M, Passos RMA, Assis LH, Borges NMTF, Hamerschlak N; **Methodology**: Santos FR, Paton EJA, Salvino M, Passos RMA, Assis LH, Borges NMTF, Hamerschlak N; **Formal Analysis:** Santos FR, Paton EJA, Salvino M, Passos RMA, Assis LH, Borges NMTF, Hamerschlak N; **Data Curation:** Santos FR, Paton EJA, Salvino M, Passos RMA, Assis LH, Borges NMTF, Hamerschlak N; **Project Administration** Santos FR, Paton EJA, Salvino M, Passos RMA, Assis LH, Borges NMTF, Hamerschlak N; **Writing:** Santos FR; **Supervision:** Paton EJA; **Final Approval:** Santos FR, Paton EJA.

DATA AVAILABILITY STATEMENT

All datasets are presented in the article.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

ChatGPT was used as a research tool.

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