REVIEW ARTICLE

Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a refined classification from the European society for blood and marrow transplantation (EBMT)

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Sinusoidal obstruction syndrome, also known as veno-occlusive disease (SOS/VOD), is a potentially life-threatening complication that can develop after hematopoietic cell transplantation (HCT). A new definition for diagnosis, and a severity grading system for SOS/VOD in adult patients, was reported a few years ago on behalf of the European Society for Blood and Marrow Transplantation (EBMT). The aim of this work is to update knowledge regarding diagnosis and severity assessment of SOS/VOD in adult patients, and also its pathophysiology and treatment. In particular, we now propose to refine the previous classification and distinguish probable, clinical and proven SOS/VOD at diagnosis. We also provide an accurate definition of multiorgan dysfunction (MOD) for SOS/VOD severity grading based on Sequential Organ Failure Assessment (SOFA) score.

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INTRODUCTION

Sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD; referred to as SOS/VOD hereafter) is a life-threatening complication occurring after hematopoietic cell transplantation (HCT) [1]. Clinical manifestation includes hepatomegaly, hepatalgia, fluid retention with ascites, weigh gain, transfusion refractory thrombocytopenia and jaundice. SOS/VOD usually resolves progressively within a few weeks, nevertheless, in patients with a severe form the mortality rate is very high (>80%) [2, 3]. The overall incidence of SOS/VOD can be estimated at around 5–15% but it varies considerably depending on the presence of risk factors and the conditioning regimen intensity [1, 2, 4–6].

In 2016 we published, with the European Society for Blood and Marrow Transplantation (EBMT), the revised diagnosis and severity criteria for SOS/VOD [7], and more recently a position statement on prophylactic, preemptive and curative treatment for SOS/VOD in adult patients [8]. With this background, our aim was to update knowledge regarding diagnosis, severity assessment, and treatment as well as pathophysiology of SOS/VOD in adult patients. In

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addition, given the importance of risk factors in the EBMT severity criteria, it also seems important to ascertain and update them. Of note, updating of the new EBMT classification for diagnosis and severity criteria in pediatric patients [9] is out of the scope of the current paper.

PATHOPHYSIOLOGY

Pathophysiology of SOS/VOD is well known. Conditioning regimens generate toxic metabolites that damage the hepatocytes and activate sinusoidal endothelial cells mainly in zone 3 of the hepatic acinus [10]. Activated sinusoidal endothelial cells swell up, leading to formation of gaps in the sinusoidal barrier. Formed elements of the blood (red blood cells and leukocytes) as well as cellular debris can then pass through these gaps between endothelial cells into the space of Disse and dissect the endothelial lining. This results in a progressive narrowing of the venous lumen, a reduced sinusoidal venous outflow, and ultimately post-sinusoidal portal hypertension [1].

Given the central role of endothelial dysfunction and microthrombus formation in SOS/VOD pathophysiology, an endothelial related biomarker panel was investigated for prediction or diagnosis of SOS/VOD. Akil et al. first reported a biomarker panel that included L-ficolin, hyaluronic acid, and vascular cell adhesion molecule-1, measured on the day of graft infusion to identify patients with high-risk SOS/VOD, and a second biomarker panel including circulating soluble suppressor of tumorigenicity-2, angiopoietin-2, L-ficolin, hyaluronic acid, and vascular cell adhesion molecule-1 for the diagnosis of this complication [11]. Nevertheless, validation and clinical implementation of these non-routine biomarkers remain to be established.

More recently, use of the endothelial activation and stress index (EASIX) biomarker panel, based on lactate dehydrogenase, creatinine, and thrombocytes, was investigated for prediction of SOS/VOD in two independent cohorts ($n = 446$ and $n = 380$) [12]. In both cohorts, EASIX assessed at the day of allogeneic (allo) HCT (EASIX-d0) was significantly associated with SOS/VOD incidence ($p < 0.0001$), overall survival (OS), and non-relapse mortality (NRM). Overall, based on routine parameters, EASIX-d0, seems to be a promising biomarker to identify populations at high risk of SOS/VOD and studies analyzing correlation with established SOS/VOD risk factors and severity would be important in order to establish how EASIX-d0 can be implemented in routine practice for SOS/VOD diagnosis, severity grading, and treatment initiation.

RISK FACTORS

Accurate definition of SOS/VOD risk factors is indispensable, particularly since they are taken into account in the severity grading (patients with two or more risk factors are classified in the upper grade) [7]. So far, we have distinguished between transplant-, patient and disease-related, and hepatic-related risk factors. Nevertheless, this approach does not provide information to manage risk factors. Therefore, we would like to propose to classify risk factors as modifiable or unmodifiable to provide some guidance on reducing risk factors and improving patients' management (Table 1). Risk factors were updated in 2020 [8] and no new evidence has been published since that time. Therefore, while the list of risk factors is almost the same, they are updated as modifiable or unmodifiable to help in the management of the patients. The only pending question concerns treosulfan which has been approved by the European Medicines Agency (EMA) for conditioning regimens. There is an important lack of information regarding the risk of SOS/VOD in adult patients receiving treosulfan-based conditioning. Nevertheless, since treosulfan is a hydrophilic analogue of busulfan, treosulfan should be considered as a risk factor for SOS/VOD in adults, similar to busulfan, until additional evidence regarding its exact impact becomes available.

DIAGNOSIS CRITERIA

For a very long time, two definitions of SOS/VOD have coexisted, based on the Seattle criteria, reported by McDonald et al. in [13], and the Baltimore criteria, reported by Jones et al. in [14]. While these definitions were used (with minor clarifications/modifications [15–17]), in clinical practice and in research studies [3, 15], they were not suitable for early diagnosis and they missed late onset SOS/VOD. Therefore, in 2016 we published the EBMT revised criteria for SOS/VOD. Since hyperbilirubinemia and jaundice are almost invariably present in classic SOS/VOD in adult patients [8], we decided to keep the classical original Baltimore criteria for diagnosis of classical SOS/VOD (within 21 days after HCT) in the revised EBMT criteria [7]. Indeed, contrary to the Seattle criteria, bilirubin ≥2 mg/dL is mandatory in the Baltimore criteria. In addition, we distinguish late-onset SOS/VOD (beyond day 21), where hyperbilirubinemia is less consistent and therefore not mandatory for diagnosis, provided patients present with at least two clinical manifestations (hyperbilirubinemia, painful hepatomegaly, weight gain >5%, and/or ascites) as well as hemodynamic and/or ultrasound evidence of SOS/VOD.

While those criteria have been recently established and no data suggest they should be challenged, we would like to acknowledge that early diagnosis of SOS/VOD can remain difficult in some patients who do not fulfill all SOS/VOD criteria, despite having severe disease. This situation can lead to a delayed initiation of treatment, particularly with defibrotide, that may have life-threatening consequences. Therefore, we would like to update the previously published revised EBMT criteria, with the addition of a new category of probable SOS/VOD diagnosis. Probable SOS/VOD would be defined by two of more of the following 5 criteria, hyperbilirubinemia, painful hepatomegaly, weight gain >5%, ascites and/or ultrasound and/or elastography suggestive of SOS/VOD (Table 2). SOS/VOD diagnoses based on the previously published EBMT SOS/VOD criteria: association of hyperbilirubinemia with 2 of the following criteria (painful hepatomegaly, weight gain >5%, and/or ascites) will be considered as clinical SOS/VOD, and histologically or hemodynamically proven SOS/VOD will be considered proven SOS/VOD.

Importantly, these criteria overlap with the revised EBMT criteria for late onset SOS/VOD, therefore, the distinction probable/clinical/proven will also be applied and the only difference for diagnosis between classical and late onset SOS/VOD will be time of onset (up to day 21 or after day 21).

Diagnostic imaging techniques include hemodynamic, ultrasound and elastography. Measurement of the hepatic venous pressure gradient (HVPG) through the jugular vein is the most accurate method to confirm the diagnosis of SOS/VOD, since an HVGP ≥ 10 mmHg has an extremely high specificity and sensitivity for SOS/VOD diagnosis in patients without previous liver disease [18–21]. However, this technique is invasive, requires experienced staff, and is not routinely available in most centers. Therefore, non-invasive techniques have been developed including ultrasound and elastography. Ultrasound can detect non-specific abnormalities in SOS/VOD including hepatomegaly, splenomegaly, gallbladder wall thickening, ascites, and portal venous flow abnormalities [22, 23]. A decrease in velocity or reversal of the portal venous flow are considered more specific for SOS/VOD, but are inconsistent and usually occur late in the disease [22–24]. Importantly, in a study among 106 patients post alloHCT, including 10 (9.4%) diagnosed with SOS/VOD, a novel ultrasound scoring, HokUS-10, was established that consisted of 10 parameters [25]. The sensitivity and specificity were 100% and 95.8%, respectively. While this score remains to be validated in a larger cohort, it can be useful for ultrasound assessment of SOS/VOD. Of

Table 1. Unmodifiable and modifiable SOS/VOD risk factors (adults).

Unmodifiable risk factors (In bold the factors with the highest relative risk)
Second HCT
Advanced disease (beyond second CR or relapse)
Primary immunodeficiency diagnosis
Genetic factors (GSTM1 polymorphism, C282Y allele, *MTHFR* 677CC/1298CC haplotype)
Older patient age
Increased serum transaminase
Karnofsky score below 90%
Metabolic syndrome
Female receiving norethisterone
Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin
Hepatotoxic drugs
Iron overload (>1.000 ng/mL)
Serum bilirubin > 1.5 mg/l (>26 µmol/l), Transaminase >2.5 ULN
Pre-existing liver disease: hepatic fibrosis, cirrhosis, active viral hepatitis
Abdominal or hepatic irradiation
Modifiable risk factors and recommendable preventive measures
Conditioning:
High dose (myeloablative) regimens
Oral or high dose busulfan
High dose treosulfan
High dose TBI-based regimen
Donor:
Unrelated donor
HLA-mismatched donor
GVHD prophylaxis:
Sirolimus + methotrexate + tacrolimus
Methotrexate + cyclosporin or tacrolimus
Non T-cell depleted transplant
Use of parenteral alimentation:
Use of parenteral nutrition

HCT hematopoietic cell transplantation, *CR* complete remission, *HLA* human leucocyte antigen, *TBI* total body irradiation, *ULN* upper limit of normal, *GVHD* graft-versus-host disease

Table 2. SOS/VOD criteria for diagnosis (adults).

Probable	Clinical	Proven
Two of the following criteria must be present: -Bilirubin ≥2 mg/dl -Painful hepatomegaly -Weight gain >5% -Ascites -Ultrasound and/or elastography suggestive of SOS/VOD	Bilirubin ≥2 mg/dl and two of the following criteria must be present: -Painful hepatomegaly -Weight gain >5% -Ascites	Histologically proven SOS/VOD or hemodynamically proven (HVPG ≥10 mmHg)
Onset		
In the first 21 days after HSCT: classical SOS/VOD	>21 days after HSCT: late onset SOS/VOD	

For any patient, these symptoms/signs should not be attributable to others causes.

note, there is a direct correlation between the hepatic arterial early acceleration index and HVPG [26], which could be helpful for SOS/VOD diagnosis. Nevertheless, this non-invasive technique requires expertise, and is not available routinely.

Liver stiffness measurement (LSM) has been reported as a possible surrogate for portal hypertension and its complications and prompted evaluation of this technique for diagnosis of SOS/VOD. Colecchia et al. used transient elastography to evaluate LSM in a cohort of 78 patients before alloHCT and at days +9/10, +15/17, and +22/24 after alloHCT [27]. Four patients developed SOS/VOD at a median time of +17 days after alloHCT and a sudden increase in LSM compared with previously assessed values and pre-HCT values was seen in all patients who developed SOS/VOD. Interestingly, LSM values did not increase significantly in patients experiencing

Table 3. Severity grading of SOS/VOD in adults.

	Mild[a]	Moderate[a]	Severe	Very severe – MOD[b]
Time since clinical symptoms of SOS/VOD	>7 days	5–7 days	≤4 days	Any time
Bilirubin (mg/dl)	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin kinetic			Doubling within 48 h	
Transaminases	≤2 × normal	>2 and ≤5 × normal	>5 and ≤8 × normal	>8 × normal
Weight increase			≥5%	≥10%
Renal function (creatininemia)	Baseline at transplant	<1.5 × baseline at transplant	≥1.5 and <2 × baseline at transplant	≥2 × baseline at transplant or diagnosis of MOD[b]

Patients belong to the category that fulfilled 2 or more criteria. If patients fulfilled 2 or more criteria in 2 different categories, they must be classified in the most severe category between both.

[a]In case of presence of 2 or more risk factors for SOS/VOD, patients should be in the upper grade.

[b]Patients with multiple organ dysfunction (MOD) must be classified as very severe, MOD is defined as ≥2 organs from the SOFA score with a score ≥2 or an increase ≥2 or organ dysfunction for patients with underlying organ involvement (Table 4).

hepatobiliary complications (according to the Common Terminology Criteria) other than SOS/VOD. The sensitivity and specificity of increased LSM over pre alloHCT for SOS/VOD were 75% and 98.7% respectively. LSM gradually decreased following successful specific SOS/VOD treatment. These findings were confirmed by another group that performed transient elastography before alloHCT, at day +7 and day +14 in 146 patients [28]. They found that a significant increase at day +14 allowed early detection of SOS (AUROC = 0.84, $p = 0.004$) with a high sensibility (75%) and specificity (99%). LSM can also be evaluated through magnetic resonance imaging (MRI) and increased LSM using magnetic resonance elastography was also reported in patients that developed SOS/VOD after chemotherapy treatment with oxaliplatin, further confirming the role of LSM for SOS/VOD diagnosis [29].

Use of other imaging techniques, including computed tomography scans and MRI scans have been investigated in SOS/VOD with no specific findings [30].

Overall, elastography for LSM is sensitive and specific for SOS/VOD diagnosis and is relevant for inclusion in the SOS/VOD diagnostic criteria in addition to hemodynamic and/or ultrasound techniques.

SEVERITY GRADING

According to the EBMT, SOS/VOD is graded in 4 stages of severity: mild, moderate, severe, and very severe, based on the following parameters: time since first clinical manifestation of SOS/VOD, bilirubin level and kinetics, transaminase level, weight gain, and renal function (Table 3). In the presence of 2 of more risk factors patients are classified in the upper grade. These criteria were validated by Yoon et al. in a group of 203 patients with SOS/VOD [31]. In these patients, very severe SOS/VOD was associated with a significantly lower OS than the others (58.6% versus 89.3%, $p < 0.0001$) and a higher day +100 transplant-related mortality, being 36.7%, versus 8.3% in mild, 8.0% in moderate and 2.7% in severe ($p < 0.0001$).

These criteria must be applied once the diagnosis of SOS/VOD is performed according to the revised EBMT diagnosis criteria and can be applied for probable, clinical, or proven SOS/VOD. It is important to evaluate SOS/VOD severity at diagnosis, nevertheless, in some patients SOS/VOD worsens and we must clearly indicate when we assign SOS/VOD severity grading whether we consider severity at diagnosis or the overall highest severity grade, irrespective of the timing of the grading.

We also would like to clarify the definition of multiple organ dysfunction/ multiple organ failure (MOD/MOF). This is particularly important since patients with SOS/VOD that develop MOD/MOF will be classified as very severe. MOD was first defined as the development of a potentially reversible physiologic derangement involving two or more organ systems not involved in the disorder that resulted in intensive care unit admission, and arose in the wake of a potentially life-threatening physiologic insult [32]. Importantly MOD should be preferred over MOF, therefore the term MOF has now been dropped. The Sequential Organ Failure Assessment (SOFA) [33] score is the standard with which to evaluate MOD, being defined as ≥2 organs from the SOFA score with a score ≥2 or an increase ≥2 of organ dysfunction for patients with underlying organ involvement. SOFA takes into account respiration, coagulation (platelet level), liver function (bilirubin level), cardiovascular function, central nervous system and renal function (Table 4). Intensive care units routinely use the SOFA score, and it can be helpful in patient assessment, particularly regarding the respiratory and cardiovascular systems. Importantly, most patients already have coagulation failure with low platelet levels at time of SOS/VOD diagnosis and SOFA assessment, therefore it should be taken into account for SOFA assessment only when there is an increase ≥2 of platelet dysfunction. Most patients have a bilirubin level ≥2 mg/dL, corresponding to at least a grade 2 liver involvement in the SOFA score, indicating that for most patients, only an organ dysfunction ≥2, in addition to liver dysfunction will lead to a diagnosis of MOD and therefore very-severe SOS/VOD.

PROPHYLAXIS AND TREATMENT

Regarding SOS/VOD prophylaxis and treatment, we issued recommendations in 2020 [8] that are still accurate today. Defibrotide remains the only agent for the treatment of severe SOS/VOD and should be initiated as soon as possible in those patients. Furthermore, given that early treatment initiation is associated with a higher day +100 OS, and that moderate SOS/VOD is associated with significant mortality [34], we also recommend early initiation of defibrotide in patients with moderate SOS/VOD. For patients with mild SOS/VOD, supportive care must be pursued with close monitoring of severity criteria to allow early initiation of defibrotide in case of worsening. Importantly, defibrotide must be initiated promptly, based on severity criteria as soon as the diagnosis of SOS/VOD is confirmed, irrespective of the diagnostic status (probable, clinical, or proven). Defibrotide is administered at a dose of 25 mg/kg/day for at least 14–21 days, and until resolution of all SOS/VOD symptoms.

Regarding prophylaxis, we would like to insist on the non-pharmacologic measure to reduce SOS/VOD modifiable risk factors. For the pharmacologic measure, ursodeoxycholic acid administered from initiation of conditioning until day +90 after

Table 4. Sequential Organ Failure Assessment (SOFA) adapted from Vincent et al., [33].

Organ System, Measurement	0	1	2	3	4
Respiration PaO2/FiO2, mmHg	Normal	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation Platelets x10^3/mm^3	Normal	<150	<100	<50	<20
Liver bilirubin, mg/dL (µmol/l)	Normal	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (>204)
Cardiovascular hypotension	Normal	MAP < 70 mmHg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13–14	10–12	6–9	<6
Renal Creatinine, mg/dL (µmol/l) or Urine output	Normal	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–5.0 (300–440) or <500 mL/day	>5.0 (>440) or <200 mL/day

[a]Adrenergic agents administered for at least 1 h (doses given are in mcg/kg/min).
Abbreviations: *MAP* mean arterial pressure

transplantation is recommended in adults [35]. Regarding use of prophylactic defibrotide, a prospective randomized phase III clinical trial compared defibrotide versus best supportive care for prevention of SOS/VOD in 372 pediatric and adult patients at high risk of SOS/VOD after transplantation (NCT02851407) [36]. No significant difference was observed between defibrotide and best supportive care groups in the primary endpoint: SOS/VOD-free survival at day +30 (67% versus 73% respectively, $p = 0.85$). Importantly, there were no differences in adverse events between groups.

CONCLUSION

Revised EBMT diagnostic and severity criteria for SOS/VOD published in 2016 allowed for the lack of specificity and sensitivity of the previous criteria. Nevertheless, some patients do not fulfill all diagnostic criteria at the early stage despite fulfilling severity criteria. The introduction of the concept of probable, clinical and proven SOS/VOD will overcome this limitation, while reconciling classical and late onset SOS/VOD. Furthermore, it seems important to include LSM with elastography in those criteria. Finally, while there have been no significant advances in SOS/VOD prevention and treatment over the last few years, better identification of risk factors in order to prevent those that are modifiable, along with an early diagnosis and treatment is probably the key to improving SOS/VOD management and patient outcomes.

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ADDITIONAL INFORMATION

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