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Selim Corbacioglu[a,*], Elias J. Jabbour[b], Mohamad Mohty[c]

[a] Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University of Regensburg, Regensburg, Germany
[b] Department of Leukemia, MD Anderson Cancer Center, Houston, Texas
[c] Department of Hematology and Cell Therapy, Acute Leukemia Working Party, European Society for Blood and Marrow Transplantation, Hôpital Saint-Antoine, Paris, France

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A B S T R A C T

Veno-occlusive disease, also known as sinusoidal obstruction syndrome (VOD/SOS), is a potentially life-threatening complication of allogeneic or autologous hematopoietic stem cell transplantation (HSCT) most commonly associated with high-intensity chemotherapies. The development of VOD/SOS may be rapid and unpredictable, and the importance of identifying risk factors to facilitate prompt diagnosis and timely treatment has become increasingly recognized. The reporting of new retrospective study data for adults and children and the emergence of novel anticancer therapies that may increase the risk of VOD/SOD also necessitate updates on risk factors, as provided in this review. The latest studies reporting VOD/SOS risk factors support previously published data, although the importance of patient-related factors, such as acute kidney injury, increased international normalized ratio, female sex (in children), and platelet refractoriness, is given greater emphasis in the recent data. Non-transplantation-related chemotherapies associated with increased risk for VOD/SOS include oxaliplatin and 5-fluorouracil chemotherapies. The novel antibody drug conjugates gemtuzumab ozogamicin and inotuzumab ozogamicin are now reported in product labeling to pose risks for VOD/SOS based on clinical trial data; an expert consensus panel has issued recommendations for risk reduction measures with inotuzumab ozogamicin treatment, including VOD/SOS prophylaxis and limitation to ≤2 inotuzumab ozogamicin treatment cycles. A wide range of biomarkers, including genetic, hematologic, hepatic, and inflammatory factors, as well as novel diagnostic techniques such as thromboelastography and measures of liver stiffness, may further enhance future risk calculation for VOD/SOS, although none has been widely adopted. Continual monitoring for and recognition of VOD/SOS risk factors are essential for optimal management of this complication.

INTRODUCTION

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication primarily associated with hematopoietic stem cell transplantation (HSCT) [1-3] and may occur in allogeneic and autologous HSCT recipients [4,5]. VOD/SOS has also been increasingly recognized to occur as the consequence of high-intensity chemotherapies in the nontransplantation setting, often in infants and young children [6-9]. The mean incidence of VOD/SOS in post-HSCT populations is estimated to be 13.7% overall, although prevalence reports have ranged widely, from 0 to 62%, in individual studies [4]. Multiorgan dysfunction (MOD) occurs in perhaps one-quarter to one-third of patients with VOD/SOS [4,10]; VOD/SOS with MOD may be associated with a mortality rate >80% post-HSCT [4].

The pathophysiology of VOD/SOS is believed to involve an initial toxic injury to the sinusoidal endothelium that triggers activation of and damage to endothelial cells, resulting in defenestration and gaps in the sinusoidal barrier [3,11,12]. This primary endothelial damage allows the extravascular deposition of red blood cells, leukocytes, and other debris into the space of Disse, which may lead to a pathophysiological cascade characterized by loss of thrombo-fibrinolytic balance, further endothelial lining dissection, downstream embolization, and occlusion of the microcirculation [2,3,11-13]. These events may lead to hepatorenal hypertension, which can result in MOD [2,3,12].

Diagnosis of VOD/SOS has been traditionally based on the Baltimore or modified Seattle criteria, both of which assess common signs and symptoms of VOD/SOS (e.g., hyperbilirubinemia, ascites, weight gain, hepatomegaly) occurring within 3 weeks of transplantation [14,15]. However, VOD/SOS

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* Correspondence and reprint requests: Selim Corbacioglu, MD, Department of Pediatric Hematology, Oncology, and Stem Cell Transplantation, University Hospital of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany.
E-mail address: selim.corbacioglu@ukr.de (S. Corbacioglu).

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symptomatology is dynamic and variable and may be progressive; researchers have increasingly recognized the possible differences in presentation between children and adults, as well as signs and symptoms divergent from the traditional criteria [3,16]. These insights are incorporated in updated criteria from the European Society for Blood and Marrow Transplantation (EBMT) for diagnosing VOD/SOS (Table 1) and assessing its severity in adults and children (Tables 2 and 3) [16,17].

Although the diagnostic updates build on previously published criteria, the novel severity criteria represent a clinically useful means for prospectively assesseing VOD/SOS risks and prognosis [1,4,15-19]. The current EBMT severity criteria for adults (Table 2) [17] and children (Table 3) [16] suggest prognostic pathologic and clinical signs and symptoms. A separate expert consensus report on supportive care for children and adolescents with VOD/SOS noted that VOD/SOS with MOD is associated with hepatocyte necrosis, which heralds advanced-stage hepatic damage signified by leakage of transaminases and other liver-specific enzymes, such as glutamate dehydrogenase [20].

These advances in VOD/SOS diagnosis and assessment reflect the accumulating evidence that early intervention is associated with improved overall survival. Consequently, they have placed a renewed emphasis on prompt and even preemptive treatment of this condition [20] and have spurred novel perspectives on risk assessment and its role in VOD/SOS management [21-23]. A number of widely recognized risk factors for VOD/SOS onset have been established from several decades of study data (Table 4) [17,24]. However, not all studies support these risk factors, whereas other investigations are continually revealing novel risk factors not previously observed or reported. This review investigates the latest data on risk factors for VOD/SOS development and progression, as well as perspectives on how to incorporate such data in VOD/SOS management.

Table 1
EBMT Criteria for VOD/SOS Diagnosis in Adults and Children [16,17]

Adult Criteria	
Classical VOD/SOS (Baltimore Criteria)	Late-Onset VOD/SOS
• Onset in the first 21 days after HSCT	• Onset beyond day 21 post-HSCT
• Bilirubin ≥2 mg/dL plus 2 or more of:	• Classical VOD/SOS (Baltimore criteria)
• Painful hepatomegaly	**OR**
• Weight gain >5%	• Histologically proven VOD/SOS
• Ascites	**OR**
	• Two or more of the following:
	• Bilirubin ≥2 mg/dL (or 34 μmol/L)
	• Painful hepatomegaly
	• Weight gain >5%
	• Ascites
	AND
	• Hemodynamic and/or ultrasound evidence of VOD/SOS
Pediatric Criteria	
• No limitation for time of onset of VOD/SOS	
• Presence of ≥2 of the following*:	
• Unexplained consumptive and transfusion-refractory thrombocytopenia†	
• Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics or a weight gain >5% above baseline value	
• Hepatomegaly‡ (best if confirmed by imaging) above baseline value	
• Ascites‡ (best if confirmed by imaging) above baseline value	
• Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥2 mg/dL within 72 h	

CT indicates computed tomography; MRI, magnetic resonance imaging.
* With the exclusion of other potential differential diagnoses.
† ≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.
‡ Suggested: imaging (ultrasound, CT, or MRI) immediately before HSCT to determine baseline value for both hepatomegaly and ascites.

IMPORTANCE OF VOD/SOS RISK CALCULATION

Identification of patients at highest risk for VOD/SOS may be key to prompt diagnosis and optimal management of VOD/SOS [25]. Several analyses have shown an association between diagnosis using the modified Seattle criteria and better outcomes versus outcomes in patients diagnosed with the more stringent Baltimore criteria [23,26,27]. In a retrospective multicenter observational study of allogeneic HSCT recipients in Japan (n = 4290), VOD/SOS with MOD was associated with higher levels of total bilirubin, ascites, and encephalopathy at diagnosis, and patients who met the Baltimore criteria had lower rates of complete response to treatment (resolution of VOD/SOS and, if present, MOD) and overall survival compared with those who met the Seattle criteria alone in either the presence or absence of MOD ($P < .001$ for all comparisons) [26]. Similarly, retrospective data from an expanded-access study of defibrotide for treating patients with VOD/SOS (with or without MOD) showed lower day +100 overall survival in HSCT recipients diagnosed by the Baltimore criteria (58.9%) compared with those diagnosed by the modified Seattle criteria (72.3%) or biopsy (67.6%) [23]. In addition, an open-label, randomized controlled trial of defibrotide prophylaxis for VOD/SOS in high-risk children undergoing HSCT found that among patients who developed VOD/SOS, those with hyperbilirubinemia (satisfying the Baltimore criteria) had a 28% higher risk of MOD compared with those without elevated bilirubin levels ($P = .04$) [23].

The key difference between these 2 diagnostic standards is the requirement for hyperbilirubinemia in the Baltimore criteria, which is included but not required under the modified Seattle criteria [14,15]. Thus, the data showing worse outcomes for patients diagnosed with VOD/SOS using the Baltimore criteria suggest that waiting for presence of hyperbilirubinemia before diagnosis and treatment may result in patients progressing to more severe disease, leading to worse outcomes [23].

Hyperbilirubinemia may be absent in up to 30% of children with VOD/SOS, including some severe pediatric cases of VOD/SOS [28]. In addition, a recent analysis from an expanded access program found that up to 13% of adults with VOD/SOS were anicteric at diagnosis, including some diagnosed within 21 days post-HSCT [29]. A retrospective study in children undergoing HSCT (n = 87) in Denmark found that the updated EBMT criteria, which do not require hyperbilirubinemia within 21 days post-HSCT (Table 1), demonstrated higher sensitivity for identifying VOD/SOS than either the modified Seattle or Baltimore criteria [28]. A large Italian study in 5072 children undergoing HSCT at 13 centers found that retrospective use of the EBMT criteria was superior to the Seattle and Baltimore criteria in identifying patients in need of treatment for severe VOD/SOS, although the EBMT identified a relatively low overall cumulative VOD/SOS incidence of 2% [30], compared with previous study data showing a VOD/SOS incidence of 20% to 30% in the pediatric HSCT population [4,15,19,30]. The study authors suggested that use of the EBMT criteria may have omitted mild and moderate cases of VOD/SOS, accounting for the low incidence of VOD/SOS in this population, or that lower-risk conditioning regimens, better

Table 2
Proposed EBMT Scale for Grading VOD/SOS Severity in Adults

Clinical Measure: Highest Grade with ≥2 Symptoms	Mild	Moderate	Severe	Very Severe: All Patients with MOD/MOF
Days since first VOD/SOS symptoms*	>7	5-7	≤4	Any time
Bilirubin, mg/dL	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin, μmol/L	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics	—	—	Doubling within 48 h	—
Transaminases	≤2× normal	>2 and ≤5× normal	>5 and ≤8× normal	>8× normal
Weight above baseline	>5%	≥5% and <10%	≥5% and >10%	≥10%
Renal function	<1.2× baseline at transplantation	≥1.2 and <1.5× baseline at transplantation	≥1.5 and <2× baseline at transplantation	≥2× baseline at transplantation or other signs of MOD/MOF
Risk factor adjustment†		Mild + ≥2 risk factors	Moderate + ≥2 risk factors	
Treatment options to consider [25]	• Maintain fluid and sodium balance • Avoid hepato/nephrotoxic drugs • Careful use of diuretics • Symptomatic treatment: analgesia, oxygen, thoracentesis, paracentesis (remove <1 L/day ascites to avoid reduced renal flow) • Progression of symptoms justifies pharmacologic VOD/SOS therapy	Mild treatments plus: • If symptoms/signs persist or progress after 2 days, start pharmacologic VOD/SOS therapy • If hemodynamic data are available, start pharmacologic VOD/SOS therapy for patients with hepatic venous gradient pressure ≥10 mm Hg	Moderate treatments plus: • Start pharmacologic VOD/SOS therapy	Severe treatments plus: • Hemodialysis/ hemofiltration if required

MOF indicates multiorgan failure.
* Time from the date when the first signs/symptoms of VOD/SOS began to appear (determined retrospectively) and the date when the symptoms met VOD/SOS diagnostic criteria.
† In the presence of ≥2 risk factors, severity is considered 1 grade higher. Adapted from Richardson et al [95] with permission.

Table 3
Proposed EBMT Scale for Grading VOD/SOS Severity in Pediatric Patients

Clinical Measure	Mild	Moderate	Severe	Very Severe: All Patients with MOD/MOF
CTCAE	1	2	3	4
Liver function tests* (ALT, AST, GLDH)	≤2× normal	>2 and ≤5× normal	>5× normal	
Persistent RT, d*	<3	3-7	>7	
Bilirubin, mg/dL*,†	<2		≥2	
Bilirubin, μmol/L,	<34		≥34	
Ascites*	Minimal	Moderate	Need 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)	Absent or <2 L/min	>2 L/min	Need for ventilator support (including CPAP)	
Central nervous system	Normal	Normal	Normal	New-onset cognitive impairment

Patients who meet criteria in different categories must be classified in the most severe category; the kinetics of the evolution of cumulative symptoms within 48 h predicts severe disease.
ALT indicates alanine transaminase; AST, aspartate transaminase; CPAP, continuous positive airway pressure; CTCAE, Common Terminology Criteria for Adverse Events; GFR, glomerular filtration rate; GLDH, glutamate dehydrogenase; RT, refractory thrombocytopenia.
* Presence of ≥2 of these criteria qualifies for an upgrade to very severe VOD/SOS.
† Preexistent hyperbilirubinemia due to primary disease was excluded. Adapted from Corbacioglu S et al [16] as licensed under a Creative Commons Attribution Noncommercial-No Derivatives 4.0 International License.

supportive treatments, and use of defibrotide as prophylaxis may explain the lower rate [30].

Earlier rather than delayed defibrotide treatment for VOD/SOS is also associated with improved outcomes, which further emphasizes the importance of risk assessment and early detection. A retrospective analysis from an open-label study in 45 children (aged .2 to 20 years) with VOD/SOS [31] found that among patients with complete response to treatment, the median postdiagnosis delay to initiation of defibrotide was approximately 1 day in patients with complete response versus 5.5 days in patients without complete response in subgroups with and without MOD ($P < .01$) [31]. A post hoc

Table 4
Reported Risk Factors for Development of VOD/SOS [6,24]

Patient-Related Factors	OR	Transplantation-Related Factors	OR
Young age [5,24]	1.7-9.5	Allogeneic HSCT [24]	2.8
Preexisting hepatic condition		Unrelated/HLA mismatch [24]	1.4
Previous liver disease [24]	3.4		
Elevated AST/ALT pre-HCST [24]	2.4-4.6		
Hepatitis C-positive [26]	2.2		
Underlying diagnosis		Previous HSCT [24]	1.9
Leukemia [24]	2.2		
Previous treatment		High-intensity/MAC regimens	2.3-7.9
Gemtuzumab ozogamicin [24]	19.8	Busulfan plus cyclophosphamide [24]	3.9-5.1
Inotuzumab ozogamicin [6],*	22	Fludarabine [24]	4.0
		TBI-based [26]	1.73
		Busulfan-based [26,30]	2.43
		Busulfan-thiotepa [36]	8.8
Previous abdominal radiation [24]	2.9	Total body irradiation [24]	
		>12 Gy plus cyclophosphamide	2.8
Impaired pulmonary function [24]	2.4	GVHD prophylaxis [24]	
Genetic predisposition [24]		Sirolimus + methotrexate + tacrolimus	~3
GSTM1 null genotype	4.1	Methotrexate + cyclosporine	3.3
KPS score <90% [24]	2.7	Cyclosporine	4.2
Ferritin >1000 ng/mL pre-HSCT [24]	3.1	Horse ATG [37]	3.5
Ferritin ≥950 ng/mL pre-HSCT [36]	8.8		
Sepsis post-HSCT [24]	4.1	Trough serum tacrolimus levels above target range (5-10 ng/mL) [21]	NR
ECOG performance status 2-4 (vs 0-1) [26]	1.9	Early day of neutrophil engraftment [5]	1.4
Advanced disease status [26]	1.5-1.7		
Acute kidney injury [21]	NR		
Platelet refractoriness [21]	NR		
High INR [21]	NR		

ATG indicates antithymocyte globulin; ECOG, Eastern Cooperative Oncology Group; GVHD, graft-versus-host disease; INR, international normalized ratio; KPS, Karnofsky Performance Status; MAC, myeloablative conditioning; NR, not reported; OR, odds ratio; TBI, total body irradiation.
* Calculated based on data from Kantarjian et al 2017 [6].

analysis of results from an expanded-access treatment (T-IND) program with defibrotide for post-HSCT patients with VOD/SOS (with and without MOD; n = 1000) found that earlier post-diagnosis initiation of defibrotide correlated with higher day + 100 survival rates over time (nominal $P < .001$) [32].

Indeed, based on the apparent value of prompt treatment, some researchers have suggested that consideration of initial pharmacologic treatment should begin at the first signs/symptoms of possible VOD/SOS even if patients have not yet exhibited all criteria for formal diagnosis [21,25]. However, defibrotide is approved only for the treatment of hepatic VOD/SOS post-HSCT in patients with renal or pulmonary dysfunction (in the United States), or severe hepatic VOD/SOS post-HSCT in adults and children age >1 month (in the European Union) [33]. Ursodeoxycholic acid is not approved for prophylaxis of VOD/SOS, and no therapies other than defibrotide and supportive measures for maintaining fluid and sodium balance are recommended for VOD/SOS treatment [3,19]. It is worth noting that defibrotide is currently the sole medication approved for VOD/SOS [33], and there is little evidence of other emerging therapies for VOD/SOS under development. A pooled analysis of clinical trials found that among HSCT recipients treated for VOD/SOS with defibrotide at or close to the approved dose of 25 mg/kg/day, day +100 survival following HSCT was 56% (95% confidence interval [CI], 49% to 63%) overall, including rates of 44% (95% CI, 35% to 52%) in patients with MOD and 71% (95% CI, 67% to 75%) in patients without MOD [34].

Researchers have also found that diagnosis and management are variable among HSCT and critical care clinicians, suggesting the need for greater standardization of risk assessment and diagnosis [35]. To help address this issue, a method for VOD/SOS risk calculation/scoring using widely recognized risk factors and supported in part by the Center for Blood and Marrow Transplant Research (CIBMTR) has been published [22]. An online risk calculator using this method is hosted on the CIBMTR website (https://www.cibmtr.org/ReferenceCenter/Statistical/Tools/Pages/VOD.aspx). The calculator was tested against VOD/SOS incidence in 13,097 HSCT recipients in the CIBMTR database and has been shown to stratify risk levels among patients. Risk factors included in this tool include age, Karnofsky Performance Status score, sirolimus use, hepatitis B/C status, type of conditioning regimen (>20 variations listed), and primary disease associated with HSCT. However, the creators of this instrument acknowledge that risk score analysis will need to be adjusted in the light of new research and changes in clinical practice [22]. The instrument is also not yet adapted for children.

RECENT STUDIES OF RISK FACTORS FOR VOD/SOS IN HSCT RECIPIENTS

Studies that evaluated risk factors for VOD/SOS in large HSCT recipient populations over the past 5 to 7 years vary in consistency with previous data and reveal potential risk factors that have not previously been noted [21,23,26,36-39] (Table 5). Among 10 such studies identified for this review, with total numbers ranging from 75 to 5072 patients, incidence of VOD/SOS ranged from 2.0% (lowest incidence was diagnosed with

Table 5
VOD/SOS Risk Factors in Selected Recent Studies in HSCT Populations

Study	Total N	Age Category	Disease Group(s)	Transplantation Type(s)/ Auxiliary Treatments*	VOD/SOS Incidence, n (%)	Transplantation-Related VOD/ SOS Risk Factors	Patient/Hepatic-Related VOD/ SOS Risk Factors
Corbacioglu et al, 2012† [23]	356	Pediatric	Hematologic cancers; neuroblastoma; soft tissue sarcoma; osteopetrosis	Multiple/MAC regimen, prophylaxis with DF (n = 180) vs controls (no prophylaxis; n = 176)	57 (16.0); 22 (12) DF prophylaxis group; 35 (20) controls	Preexisting liver disease/complications; diagnoses of inherited HLH; osteopetrosis	Second myeloablative HSCT; allogeneic HSCT for leukemia beyond second relapse; busulfan and melphalan conditioning; previous GO treatment; GO
Kim et al, 2013 [37]	260	Adult	Idiopathic aplastic anemia	Allogeneic	19 (7.3)	Cyclophosphamide‡; horse ATG§	None
Tsirigotis et al, 2014 [38]	271	Adults and adolescents	Hematologic cancers	Allogeneic/RIC	24 (8.8)	Busulfan i.v. reduced VOD/SOS risk vs oral administration§	None
Maximova et al, 2014 [39]	200	Pediatric	Hematologic cancers; solid tumors; immunodeficiencies; IEM	Multiple; VOD/SOS; prophylaxis with UA; DF	34 (17)	Tacrolimus for GVHD prophylaxis instead of cyclosporine reduced VOD/SOS risk‖	Ferritin >1000 ng/mL pre-HSCT;§ sepsis post-HSCT§
Yakushijin et al, 2016 [26]	4290	Adult	Hematologic cancers	Multiple	462 (10.8)	MAC regimens (TBI-based and busulfan-based)§; ≥2 HSCTs vs 1 HSCT§	ECOG performance status 2-4 (vs 0-1)‡; hepatitis C positive§; advanced disease status§
Roeker et al, 2019 [21]	1823	Adult	NR	Multiple/MAC regimen	205 (11.2)	Trough serum tacrolimus levels above target range (5-10 ng/mL)§	Acute kidney injury§; platelet refractoriness§; high INR§
Hwang et al, 2016 [36]	132	Adult	Malignant lymphoma	Autologous/heparin and UA for VOD/SOS prophylaxis	10 (7.6)	Busulfan-thiotepa§	High pre-HSCT ferritin serum level (≥950 ng/mL)§
Abate et al, 2018 [40]	75	Adult and pediatric	High-risk Ewing sarcoma	Autologous/i.v. busulfan and melphalan conditioning	5 (6.7)‖	Previous radiation therapy‡	None
Schechter et al, 2018 [5]	75	Pediatric	High-risk neuroblastoma	Autologous/i.v. busulfan and melphalan conditioning	23 (30.7)	None	Young age§; early neutrophil engraftment§
Faraci et al, 2019 [30]	5072	Pediatric	Hematologic cancers; solid tumors; nonmalignant	Multiple/DF or UA prophylaxis used in some patients	103 (2.0)¶	Busulfan§; melphalan‡	Female sex§; age <2 y at HSCT§; diagnosis of HLH§; diagnosis of neuroblastoma or thalassemia‡

DF indicates defibrotide; HLH, hemophagocytic lymphohistiocytosis; IEM, inborn errors of metabolism; RIC, reduced-intensity conditioning; UA, ursodeoxycholic acid.

* Transplants and auxiliary treatments are specified when uniform for all patients; otherwise, multiple conditioning or prophylactic regimens were used.

† All patients were considered high-risk for VOD/SOS based on listed risk factors (columns 7 and 8); the high incidence of VOD/SOS (20%) in the control (nonprophylaxis group) confirmed the validity of these risk factors.

‡ Following univariate analysis only.

§ Following multivariate analysis.

‖ Moderate to severe VOD/SOS, all cases in adults (0 cases in 32 pediatric patients).

¶ Diagnosed according to the 2018 EBMT criteria for VOD/SOS in children.

EBMT criteria) to 30.7% (Table 5). Transplantation-related factors associated with an increased risk of VOD/SOS in adult HSCT recipients following multivariate analysis included the use of horse antithymocyte globulin [37], oral versus i.v. serum level-adjusted administration of busulfan (adults and adolescents) [38], myeloablative conditioning regimens (total body irradiation-based and busulfan-based) and 2 or more HSCTs [26], use of busulfan-thiotepa conditioning in adults with VOD/SOS requiring pharmacologic treatment with at least analgesics or diuretics [36], and increased trough serum tacrolimus level (above the target range of 5 to 10 ng/mL) [21]. In children, the use of busulfan in conditioning regimens versus nonuse of busulfan was an independent risk factor for VOD/SOS, diagnosed with the EBMT pediatric criteria in a large study (n = 5072), associated with a cumulative incidence of 5.1% (95% CI, 4.1% to 6.3%; $P < .001$) [30]. The 90 patients given busulfan who developed VOD/SOS included 5 of the 35 (14.2%) who received oral busulfan and 10 of the 55 (18.1%) who received i.v. busulfan. Pharmacokinetics of plasma busulfan were monitored in all patients.

Risk factors for VOD/SOS identified in these studies following univariate, but not multivariate, analysis included cyclophosphamide in an adult study [37] and previous radiation therapy in adults (but not in children in the same study) with high-risk Ewing sarcoma [40]. Transplantation-related factors that reduced the risk of VOD/SOS were reported in 2 pediatric studies [30,39]. These included the use of tacrolimus instead of cyclosporine as a prophylaxis for graft-versus-host disease [39] and the use of cord blood cells as a stem cell source, although this source was used in only 6% of patients in the study [30].

Patient/hepatic-related VOD/SOS risk factors in adults, identified following multivariate analysis, included Eastern Cooperative Oncology Group Performance Status score 2 to 4 versus 0 to 1, hepatitis C seropositivity, and advanced disease status in 1 study [26]; high pre-HSCT ferritin level (≥950 ng/mL) in patients with malignant lymphoma in another study [36]; and acute kidney injury, platelet refractoriness, and high international normalized ratio in a 20-year study described as the largest single-center analysis of VOD/SOS incidence following myeloablative conditioning (n = 200) (Table 5) [21]. In pediatric studies, patient/hepatic-related VOD/SOS risk factors following multivariate analysis included a high pre-HSCT ferritin level (>1000 ng/mL) and post-HSCT sepsis [39], young age and early of neutrophil engraftment [5,22], and female sex, age <2 years, and diagnosis of hemophagocytosis lymphiocytosis [30]. In addition, the high incidence of VOD/SOS reported in a defibrotide prophylactic study [23] (16.0% overall; 20% in untreated controls; Table 5) supported the validity of previously established VOD/SOS patient- and transplantation-related risk factors in children as noted in the current British Committee for Standards in Haematology/British Society for Blood and Marrow Transplantation guideline for VOD/SOS diagnosis and management [19].

Overall, these data are generally consistent with previously recognized risk factors, although hepatic indicators were not prominent in the recent studies, and acute kidney injury and increased international normalized ratio, reported in a recent study (Table 5) [21], have not been previously recognized as important risk factors [17,24]. Platelet refractoriness, also identified as a risk factor in that study (Table 5) [21], was reported in multiple previous studies to be a risk factor for VOD/SOS incidence or morbidity/mortality [1,14,15,41]. Although i.v. administration of busulfan was found to reduce the risk of VOD/SOS versus oral busulfan administration in one adult study in this sample [38], studies in children do not support this finding [30,42]. Other studies have reported increased risk for post-HSCT VOD/SOS with high-dose busulfan/high plasma exposure to busulfan [36,43,44]. Increased VOD/SOS risk in post-HSCT patients also has been reported with pharmacokinetic monitoring of busulfan dosing, which may be related to higher plasma exposure to the drug [22].

The recently reported data demonstrate that although certain risk factors are established for VOD/SOS, independent risk factors may vary across populations and may include risks not previously noted in the literature. In addition, although review data indicate that VOD/SOS occurs most commonly after allogeneic HSCT [4], 3 recent studies (adult and pediatric) in autologous HSCT reported VOD/SOS incidence of approximately 7%, 8%, and 31% (Table 5) [5,36,40]. Other studies have also reported the incidence of VOD/SOS in patients receiving haploidentical HSCT [45,46], including delayed cases (e.g., median onset 44.5 days post-HSCT) [46].

VOD/SOS RISK FACTORS ASSOCIATED WITH NONTRANSPLANTATION-RELATED CHEMOTHERAPY

The risks of VOD/SOS outside of the HSCT setting have become more broadly recognized in recent years. For example, of 1137 patients enrolled in the expanded-access (T-IND) study who developed VOD/SOS and were treated with defibrotide, 137 (12%) had VOD/SOS associated with primary chemotherapy (non-HSCT-related) [9]. Among these patients was a clinically meaningful subgroup of 82 patients (60%) who had developed VOD/SOS and initiated defibrotide treatment within 30 days of starting chemotherapy; 66 (80.5%) of these patients were aged ≤16 years, and 38 (46.3%) had MOD. The most commonly administered chemotherapeutic agents in the 82 patients were cyclophosphamide (53.7%), cytarabine (51.2%), vincristine (47.6%), methotrexate (34.1%), and thioguanine (30.5%). Gemtuzumab ozogamicin (GO) was used in 2 patients, including 1 patient with MOD and 1 without MOD. However, the study was not powered to investigate correlations of outcomes with specific agents or regimens [9].

Among the early reports of risk factors for nontransplantation-related VOD/SOS, a pathology study assessed the incidence of severe injury in the nontumoral liver tissue due to VOD/SOS from 153 surgically resected liver metastases [46,47]. In this study, 44 (51%) of the 87 postchemotherapeutic liver resection specimens exhibited sinusoidal dilation and hemorrhage associated with rupture of the sinusoidal barrier, whereas the 66 livers treated with surgery only were normal. Perisinusoidal and veno-occlusive fibrosis also developed in 21 of the 44 postchemotherapy patients (48%), and the development of liver lesions was associated with oxaliplatin. More than three-quarters of the 43 patients treated with oxaliplatin developed lesions (n = 34; 79%), compared with less than one-quarter of the 44 patients who did not receive oxaliplatin treatment (n = 10; 23%).

A retrospective single-center study in 151 patients with colorectal liver metastases who had undergone resection of ≥1 liver segment found after multivariate analysis that oxaliplatin and 5-fluorouracil chemotherapies were associated with presence of severe lesions of VOD/SOS ($P < .001$ and $P = .005$, respectively) [48]. With regard to patient/hepatic-related risk factors, univariate analysis found that the aspartate aminotransferase:platelet ratio index and splenomegaly were associated with severe lesions of VOD/SOS. A potential association of oxaliplatin-based treatment and occurrence of VOD/SOS also was reported in 4 patients with lymphoma who underwent HSCT and had no other patient-related VOD/SOS risk factors [49].

ANTIBODY-DRUG CONJUGATES AND VOD/SOS RISK

The novel antibody-drug conjugates GO and inotuzumab ozogamicin (INO), calicheamicin conjugates targeted against CD33 and CD22, respectively, were associated with increased risk of VOD/SOS in clinical trials [6,7,17,50-53]. Black box warnings regarding the risk of hepatic VOD/SOS with use of each agent are included in their prescribing information documents [54,55]. GO was first approved in 2000 by the US Food and Drug Administration for treatment of relapsed $CD33^+$ acute myelogenous leukemia (AML), in patients aged >60 years [52]. However, in a report of 23 consecutive patients given GO for AML who relapsed following HSCT, liver injury consistent with VOD/SOS occurred in almost half (n = 11); histology studies suggested that GO toxicity resulted from its targeting of $CD33^+$ cells in hepatic sinusoids [52]. In 2010, GO was withdrawn from the market owing to an association of GO plus intensive chemotherapy with increased early deaths in patients with AML, as well as phase III clinical trial evidence showing no evidence of overall survival benefits [56,57]; it was reapproved for AML in 2017 based on efficacy and safety data for GO administered with a fractionated dosing schedule [58,59].

Among studies reporting incidence of VOD/SOS with GO, a phase III, open-label study in 26 hematology centers in France (ALFA-0701) evaluated the efficacy and toxicity of the addition of low-fractionated-dose GO to standard chemotherapy (n = 140) versus standard therapy alone (n = 140) in adults with AML [54,60]. In this study, VOD/SOS occurred in 6 of 131 (5%) evaluated patients given GO; 3 (50%) of the cases were fatal, and 5 of the cases occurred within 28 days of any dose of GO. The study investigators recommended an interval of 2 months between the last dose of GO and HSCT. A retrospective safety analysis of clinical trial data provided by a GO manufacturer's safety registry and a state/federal government pharmacovigilance initiative was conducted before the 2017 reintroduction [7]. A total of 99 (11.4%) cases of VOD/SOS were reported among 870 GO-treated patients (221 HSCT recipients and 649 non-HSCT patients). Rates of VOD/SOS were 3% when GO was administered as monotherapy at doses ≤6 mg/m^2, 28% when administered with thioguanine, 15% when administered as monotherapy at a dose of 9 mg/m^2, and between 15% and 40% when HSCT was performed ≤3 months following GO. Death from VOD/SOS occurred in 33% of the cases [7].

However, no cases of GO-associated VOD/SOS were reported in a trial in 237 patients age ≥61 years with AML unsuitable for intensive chemotherapy; this trial compared GO with best supportive care [51]. Patients received GO at 6 mg/m^2 (first induction dose) and 3 mg/m^2 (second induction dose) and could receive up to 8 monthly infusions of 2 mg/m^2 thereafter. The risk of GO-associated VOD/SOS also was assessed retrospectively in 146 adults who received GO treatment for AML before undergoing HSCT [53]. Prophylaxis for VOD/SOS was used in 69 patients (heparin, n = 57; ursodeoxycholic acid, n = 8; defibrotide, n = 4). The median GO dose was 3 mg/m^2 (range, 3 to 9 mg/m^2). The cumulative incidence of VOD/SOS was 8% (n = 11), including 3 patients who died. Neither VOD/SOS incidence nor survival differed between patients who received GO ≤3.5 months before HSCT and all other patients. The authors concluded that low-dose GO before HSCT was associated with an acceptable incidence of VOD/SOS [51].

INO is Food and Drug Administration-approved for treatment of relapsed/refractory B cell acute lymphoblastic leukemia (ALL) in adults [61,62]. The safety and efficacy of INO was assessed in 90 patients with relapsed/refractory ALL who received INO on 2 different schedules, weekly and single dose; 36 patients (40%) also underwent allogeneic HSCT [61]. In this study, VOD/SOS occurred in 1 of 14 patients (7.1%) who underwent HSCT after weekly INO and in 5 of 22 HSCT recipients (22.7%) after single-dose INO.

A phase III trial compared INO with standard intensive chemotherapy in 326 patients with relapsed/refractory ALL [6,63]. Among the 307 patients in the updated safety group [6], VOD/SOS occurred in 22 of the 164 patients (13%) who received INO versus 1 patient of the 143 (<1%) in the standard therapy group. Of 77 patients who received INO and proceeded to HSCT, 17 (22%) developed VOD/SOS, including 5 fatal cases; VOD/SOS occurred in 5 patients who did not proceed to HSCT in the INO group versus none in the standard therapy group [6]. Total all-cause grade 3-5 hepatotoxic events, including VOD/SOS, occurred in 83 (51%) of patients in the INO group versus 49 (43%) of patients given standard therapy.

Based on these data from the phase III trial of INO, an expert panel of hematologists and transplantation physicians offered recommendations for managing the risk of VOD/SOS and other hepatic adverse events with INO treatment [8]. The key recommendations of this panel were the use of prophylaxis against VOD/SOS and monitoring of symptoms; in patients for whom HSCT is anticipated, limitation of INO cycles to 2, if possible; and rendering of treatment in accordance with the EBMT position statement on VOD/SOS treatment [3]. In conclusion, the occurrence of an elevated risk for VOD/SOS with the use of antibody-drug conjugates with different targets points to a relationship with the conjugated calicheamicin, an extremely potent anthracyclin, rather than the conjugated antibodies.

BIOMARKERS

Diverse biomarkers for potential prediction and early detection of VOD/SOS have been proposed, which may prove useful, although they are not yet widely accepted (Table 6) [64]. Of these, increased plasminogen activator inhibitor-1 antigen level is perhaps the most well studied and supported [13,65-67]. However, the identified biomarkers encompass a wide array of pathogenic pathways, each with a sound rationale for investigation (Table 6) [64]. Indeed, some researchers have suggested using a panel of associated and interactive biomarkers, rather than just 1 or 2, for risk prediction [68,69]. Biomarkers of VOD/SOS have been identified for both the HSCT setting and for risks associated with primary chemotherapies, such as oxaliplatin [70,71]. However, whether biomarkers identified in these different populations will be applicable in other contexts is unclear. Given these variables, the establishment of predictive biomarkers for VOD/SOS that would be clinically practical and widely applicable currently remains elusive.

NEW DIAGNOSTIC TECHNIQUES/PARAMETERS

Researchers have also investigated the potential for various biomarkers to constitute reliable diagnostic criteria for VOD/SOS, as well as indicators of risk. From a hematologic perspective, thromboelastography is a functional assay that can assess the balance of procoagulant and anticoagulant proteins in blood vessels, and thus determine the risk for thrombosis leading to VOD/SOS or for bleeding with anticoagulant treatment [72,73]. One study found that rotation thromboelastography at day +12 following HSCT identified patients with delayed thrombin formation, which was correlated with the development of VOD/SOS [72]. Thromboelastography also has been used to assess bleeding risk in patients with VOD/SOS and guide treatment with defibrotide [73]. Novel hepatic diagnostic criteria for VOD/SOS that have been investigated include liver stiffness, measured with ultrasound or acoustic radiation force impulse shear wave elastography, as an indication of venous congestion and

Table 6
Proposed Biomarkers for VOD/SOS by Physiologic/Organ System

Biomarker	Reference(s)
Broad-spectrum/multiple mechanism	
Panel of changes in tumorogenicity-2, angiopoieten-2, L-ficolin, hyaluronic acid, and VCAM-1	[68]
↓ L-ficolin plasma level	[83]
Genetic polymorphisms	
MTHFR C677T/A1298C	[84]
Heparanase single nucleotide polymorphisms	[85]
Hematologic and endothelial	
↓ Protein C levels	[86-88]
↓ Antithrombin III levels	[13,87]
↓ Type III procollagen and tPA	[88]
↑ PAI-1 antigen levels	[13,65-67]
↑ Extra-cellular endothelial vesicles CD144^{+}	[13]
↑ vWF, thrombomodulin, soluble IAM-1*	[89]
Hepatic/splenic	
↑ Maximum total serum bilirubin/bilirubin increase at any point in time	[90]
↑ Total bilirubin, D-dimer	[67]
↑ Hepatocyte growth factors/with/without IL-6	[91]
↑ APRI	[70]
↑ Splenic volume	[71]
↑ Panel of liver fibrosis indices: API, APRI, PSR, FIB-4†	[69]
Inflammatory/immune response	
↑ IL-6, IL-10, TNF-α plasma levels‡	[92]
↑ IL-6 plasma level at + day 7 post-HSCT	[93]
↓ IGF and IGFBP-3 plasma levels	[94]

API indicates age-platelet index; APRI, aspartate aminotransferase-to-platelet ratio; FIB-4, fibrosis-4; IAM, intercellular adhesion molecule; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; PAI, plasminogen [84] activator inhibitor; PSR, platelet-to-spleen ratio; tPA, tissue plasminogen activator; vWF, von Willebrand factor; VCAM, vascular cell adhesion molecule.

* In patients receiving sirolimus.

† In patients receiving primary oxaliplatin therapy.

‡ Predicted organ dysfunction in patients undergoing transplantation; IL-10 and TNF-α were detectable in <50% of patients with organ dysfunction.

fibrosis [74-76]. Several studies have demonstrated early diagnosis or prediction of VOD/SOS with this method, before the appearance of conventional clinical criteria [74-76]. Other proposed methods involve the multifactorial, or panel, scoring approach for early diagnosis or prediction of VOD/SOS with the use of ultrasound [77-80]. Independent predictors of VOD/SOS that may enhance ultrasound diagnosis include gallbladder wall thickening and paraumbilical vein blood flow [78,80]. Proposed methods aimed at diagnosis or prediction specifically of chemotherapy-induced VOD/SOS include a score consisting of expression of CD34 cells, increased levels of smooth muscle actin, and aberrant expression of glutamine synthetase [79]. The use of contrast-enhanced computed tomography also has been suggested to detect multiple factors such as clover-like sign, peripheral distribution of heterogeneity, increased spleen volume, and hepatic parenchyma, which were found to be independent predictors of VOD/SOS via this method [77,81,82].

CONCLUSION

Multiple risk factors for VOD/SOS have been identified that should allow for expedited identification of patients at risk and for diagnosis, and a practical instrument for risk calculation has been introduced. However, collection and analysis of new evidence is ongoing, and sometimes conflicting, for markers of risk, onset, and progression of VOD/SOS. The recent advent of GO and INO use also demonstrates that new risks for VOD/SOS may arise with the use of effective but toxic anticancer therapies, and physicians should exercise caution and vigilance for VOD/SOS in the context of these treatments. Although no predictive biomarkers have been widely established and accepted, the use of such indicators should prove useful when fully supported by research. New technological approaches and diagnostic, multifactorial scoring methods also hold the promise of improving the prediction and diagnosis of VOD/SOS.

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