INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

Check for updates

doi:10.1111/imj.16453

POSITION PAPER

ANZTCT practice statement: sinusoidal obstruction syndrome/veno-occlusive disease diagnosis and management

Shaun Fleming,[1] Ashleigh P. Scott,[2] John Coutsouvelis,[3,4] Chris Fraser,[5] Ashish Bajel,[6,7] Adam Nelson,[8] Rachel Conyers,[9,10,11] Ashley McEwan,[12,13] David Yeung,[14] Victoria Campion,[15] Lochie Teague,[16] Matthew McGuire,[17] Edward Morris,[18] Melissa Gabriel,[19] Rebecca Wayte,[20] Genevieve Douglas,[21] Nicole Chien[22] and Nada Hamad[23,24,25]

[1]Clinical Haematology, Alfred Hospital and Australian Centre for Blood Diseases, and [4]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, [3]Pharmacy Department, Alfred Health, [6]Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, [7]Faculty of Medicine, Dentistry and Health Sciences, and [11]Department of Paediatrics, University of Melbourne, [9]Pharmacogenomics Team, Stem Cell Biology, Murdoch Children's Research Institute, [10]Children's Cancer Centre, The Royal Children's Hospital, and [21]Clinical Haematology, Austin Health, Melbourne, Victoria, [2]Department of Haematology and Bone Marrow Transplant, Royal Brisbane and Women's Hospital, and [5]Blood and Marrow Transplant Service, Queensland Children's Hospital, Brisbane, [18]Department of Haematology and Bone Marrow Transplantation, Townsville University Hospital, Townsville, Queensland, [8]Kids Cancer Centre, Sydney Children's Hospital, [12]Haematology Department, Liverpool Hospital, [13]South West Sydney Clinical School, Faculty of Medicine, University of New South Wales, [19]Cancer Centre for Children, The Children's Hospital at Westmead, [20]Department of Haematology, Royal Prince Alfred Hospital, [23]Department of Haematology, St Vincent's Hospital Sydney, [24]School of Clinical Medicine, Faculty of Medicine and Health, UNSW Sydney, and [25]School of Medicine, University of Notre Dame, Sydney, New South Wales, [14]Royal Adelaide Hospital and Adelaide Medical School, Adelaide, South Australia, [17]Department of Pharmacy, Fiona Stanley Hospital, Perth, Western Australia, Australia, and [15]Wellington Blood and Cancer Centre, Wellington Hospital, Wellington, and [16]Starship Blood and Cancer Center, Starship Children's Hospital, and [22]Department of Haematology, Auckland City Hospital, Auckland, New Zealand

Key words
sinusoidal obstruction syndrome/veno-occlusive disease, sinusoidal obstruction syndrome, SOS/VOD, haemopoietic stem cell transplantation.

Correspondence
Shaun Fleming, Malignant Haematology & Stem Cell Transplant Service, Department of Clinical Haematology, Alfred Hospital, Ground Floor, South Block, Alfred Hospital, 55 Commercial Road, Melbourne, Vic. 3004, Australia.
Email: s.fleming2@alfred.org.au

Received 15 January 2024; accepted 26 May 2024.

Abstract

Sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a life-threatening complication which can develop after haemopoietic stem cell transplantation (HSCT) and some antibody–drug conjugates. Several SOS/VOD diagnostic and management guidelines exist, with the most recent and refined being the European Society for Blood and Marrow Transplantation adult and paediatric guidelines. Timely diagnosis and effective management (including the availability of therapeutic options) significantly contribute to improved patient outcomes. In Australia and New Zealand, there is variability in clinical practice and access to SOS/VOD therapies. This review aims to summarise the current evidence for SOS/VOD diagnosis, prevention and treatment and to provide recommendations for SOS/VOD in the context of contemporary Australasian HSCT clinical practice.

Funding: Medical writing support was funded by Pfizer in accordance with Good Publication Practice (GPP2022) guidelines (https://www.acpjournals.org/doi/10.7326/M22-1460).
Conflict of interest: None.
Disclosures: L. Teague, V. Campion, E. Morris, A. Scott, M. Gabriel, A. Nelson, A. McEwan, R. Wayte, N. Chien and R. Conyers: No disclosures. S. Fleming: Speaker's bureau for Amgen, Pfizer; Honoraria from Servier, Abbvie, Gilead-Kite, Pfizer, Astellas, Novartis and Amgen; Advisory board membership for Pfizer, Amgen, Gilead-Kite, Novartis and Servier. A. Bajel: Speaker's bureau for Amgen; Honoraria from Abbvie, Gilead-Kite, Pfizer, Astellas, Jazz Pharma, Novartis, Takeda and Amgen. G. Douglas: Honoraria from Roche, Novartis. D. Yeung: Honoraria from Pfizer, Takeda, Novartis and Amgen; Advisory board membership for Pfizer, Amgen, Novartis, Servier; Research funding from Novartis and Bristol Myers Squibb. M. McGuire: Conference attendance, Novartis. C. Fraser: Advisory Boards Link Pharmaceuticals, Amgen. N. Hamad: Advisory board honoraria from Pfizer, Gilead-Kite, Novartis, AbbVie, Roche, Janssen, CSL, Terumo, Mallinckrodt, Jazz Pharma, Takeda, Astra Zeneca, Incyte and Sanofi. J. Coutsouvelis: Invited speaker by Jazz; Advisory board Amgen, Juniper and Abbvie.

Introduction

Sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a potentially fatal complication following haemopoietic stem cell transplantation (HSCT). SOS/VOD can also be observed in patients in the absence of HSCT following toxin exposures and has been described in patients who have received therapies with immunoconjugates such as inotuzumab ozogamicin (InO) and gemtuzumab ozogamicin (GO). SOS/VOD is primarily an acute hepatotoxicity syndrome, characterised by intrahepatic venule obstruction and damage to surrounding hepatocytes. SOS/VOD can rapidly result in liver failure and multiorgan failure, and thus affected patients are at high risk of mortality.

SOS/VOD is biologically and clinically heterogeneous, evidenced by the existence of multiple competing diagnostic criteria and treatment guidelines. In Australia and New Zealand, institutional access to SOS/VOD therapies and clinical practice varies, with the potential to impact patient outcomes. This review aims to summarise the current evidence for SOS/VOD diagnosis, prevention and treatment and to provide recommendations for SOS/VOD management in the context of contemporary Australasian HSCT clinical practice.

VOD pathophysiology and clinical manifestations

Classically, SOS/VOD presents with hyperbilirubinaemia, painful hepatomegaly and fluid retention with weight gain.[1] SOS/VOD pathophysiology is complex and incompletely understood. Activation and damage to the sinusoidal endothelial cells in zone 3 of the liver acini occur, mediated by a variable mix of chemotherapy, radiotherapy, cytokines, endogenous microbial products, drugs and diffuse endothelial damage from HSCT. Sloughed sinusoidal lining embolisms downstream, obstructing flow and eventually leading to complete venular destruction and extensive hepatic necrosis. This in turn results in the clinical manifestations of reduced hepatic outflow (non-cirrhotic portal hypertension, fluid overload and ascites) and synthetic dysfunction (coagulopathy and hyperbilirubinaemia).[2] Unless arrested, SOS/VOD results in death from fulminant hepatic failure and/or multiorgan failure. Classically, SOS/VOD occurs within the first 21 days after HSCT; however, late-onset SOS/VOD can still occur beyond 21 days.[3]

SOS/VOD risk factors

Risk factors for SOS/VOD occurrence and severity are categorised by the European Society for Blood and Marrow Transplantation (EBMT) as being transplant-related, patient and disease-related or liver-related.[3] In turn, these risk factors may be further categorised into modifiable or unmodifiable in both adult[3] and paediatric[4] populations.

Unmodifiable risk factors include patient age, disease status and genetic predisposition; single nucleotide polymorphisms in the GSTM1, MTHFR and C282Y genes are postulated to be involved in an individual sensitivity to SOS/VOD, particularly as it relates to busulfan use in HSCT conditioning.[4] Transplant-related risk factors are sometimes modifiable; myeloablative conditioning, particularly when including total body irradiation or busulfan, is potentially modifiable, but unrelated donor selection is not. Certain diseases which increase the risk of SOS/VOD are more prevalent in paediatric HSCT populations than in adults, where malignant HSCT indications are more predominant. These include haemophagocytic lymphohistiocytosis, transfusion-dependent anaemias with underlying hepatic fibrosis because of iron overload, and osteopetrosis. This may partially explain why SOS/VOD incidence is higher in children (and particularly infants) than in adults.[4]

Hepatic factors include baseline liver function, with patients who have active hepatitis or known cirrhosis at greater risk of SOS/VOD. Furthermore, pre-HSCT exposure to the antibody–drug conjugates GO and InO increases the risk of SOS/VOD.[5–7] These agents can induce SOS/VOD after administration alone or in subsequent HSCT. The phase III INO-VATE trial comparing InO to standard of care in 326 adults with relapsed or refractory acute lymphoblastic leukaemia (ALL) reported increased SOS/VOD incidence following InO (14.0%) compared to standard-of-care chemotherapy (2.1%).[7] Similarly, another study of 26 ALL patients who received allogeneic HSCT after treatment with InO also reported post-HSCT SOS/VOD incidence of 19%.[8] The INO-VATE trial also found a 6.6-fold increase in SOS/VOD incidence among patients treated with two (vs one) alkylating agents.[7,9]

SOS/VOD epidemiology

The reported incidence of SOS/VOD varies across institutions; this likely reflects not only the clinical and biological heterogeneity of the disease entity, but also differences in HSCT practices, local populations and diagnostic criteria used. Worldwide incidences in adults and children are approximately 10% and 20% respectively.[4] In Australian and New Zealand HSCT recipients, the incidence is reported as 4.1% in adults and 11.5% in children.[10] Anicteric SOS/VOD is more prevalent in children, and late presentation (>30 days after HSCT) occurs in up to 20% of paediatric SOS/VOD cases.[10–12] SOS/VOD commonly resolves within a few weeks in most patients with mild to moderate disease.[13] In severe cases, SOS/VOD

Internal Medicine Journal (2024) 1–9

can lead to multiorgan failure, with an 80% mortality rate.[11]

The incidence of SOS/VOD has been estimated to be between 15% and 40% in acute myeloid leukaemia (AML) patients when HSCT is performed within 3 months of GO administration.[14] Although the incidence of SOS/VOD reported in the GO arm in the ALFA-0701 trial was 4.6%,[15] a study of 62 AML patients also identified prior treatment with GO as a significant risk factor for SOS/VOD (odds ratio = 21.6; 95% confidence interval (CI) = 4.2–112.2).[6] Using fractionated, lower doses of GO might alleviate the increased SOS/VOD risk following HSCT; a retrospective analysis of 146 adult patients found that the incidence of SOS/VOD was not significantly higher in patients receiving a median GO dose of 3 mg/m^2 prior to HSCT than that reported in historical cohorts of patients not receiving GO.[16]

SOS/VOD diagnosis

Australian practice, defibrotide access, and incidence data reflect usage of the multiple prior SOS/VOD diagnostic criteria; this may change as we refine our diagnostic and treatment strategies. The most widely used diagnostic criteria are the Baltimore, Modified Seattle and EBMT criteria.[3,4,17,18] A criticism of the Modified Seattle[17] and Baltimore criteria[18] is a relatively poor capacity to diagnose SOS/VOD early,[3] potentially leading to poorer outcomes because of delayed treatment initiation. In this context, the EBMT published revised diagnostic and severity criteria in 2016 aimed at increasing early diagnosis and capturing late-onset SOS/VOD.[19] The EBMT criteria have since been updated two times[3,13] to promote early initiation of SOS/VOD treatment to prevent liver failure becoming established or irreversible. The most recent (2023) EBMT diagnostic and severity criteria for SOS/VOD refine the previous classification and distinguish probable, clinical and proven SOS/VOD at diagnosis.[3] They also refine the definition of multiorgan dysfunction for severity grading based on the Sequential Organ Failure Assessment score.[3]

A prospective study evaluating the EBMT 2023 criteria in paediatric patients found that it resulted in earlier diagnosis, as the incidence rate using EBMT criteria was 8.9%, whereas the incidence rate using the Modified Seattle/Baltimore criteria was 4.9%.[12] The increased rate of diagnosis using the EBMT criteria is attributed to the improved identification of mild and moderate cases, as intended, and the fact that it allows for a probable category of SOS/VOD. Use of EBMT criteria was associated with shorter duration of defibrotide treatment and reduced the length of hospitalisation by a median of 12 days.[12] Unlike the Modified Seattle and Baltimore criteria, the new adult EBMT criteria include specific criteria for a 'probable' SOS/VOD diagnosis by removing the mandatory criterion of hyperbilirubinaemia. However, the EBMT criteria still state that a clinical diagnosis of classical SOS/VOD (<21 days following HSCT) still requires elevated bilirubin of ≥2 mg/dL (34.2 μmol/L).[3]

Unlike in adults, late-onset SOS/VOD is common in children, with an estimated 20% of cases developing more than 30 days after HSCT.[4] The EBMT criteria have been developed to capture late-onset (>21 days) SOS/VOD by removing hyperbilirubinaemia as a mandatory criterion since hyperbilirubinaemia is less consistent in late-onset disease.[3] Instead, the EBMT paediatric diagnostic criteria recommend rising bilirubin from a baseline value on three consecutive days as one of the diagnostic indicators for SOS/VOD[12] (Table 1).

Although SOS/VOD is very much a clinical diagnosis, non-invasive diagnostic imaging techniques have been used as a diagnostic adjunct tool. Such techniques include grey scale ultrasound, Doppler ultrasound, contrast-enhanced ultrasound, computed tomography, magnetic resonance imaging, positron emission tomography and ultrasound elastography techniques.[20] It is noteworthy that these imaging techniques are not commonly used in SOS/VOD diagnosis. Hepatic venous-portal gradient (HVPG) measurement and contextual transjugular-liver-biopsy are considered the 'gold standard' diagnostic techniques to differentiate SOS/VOD from other pathologies such as hepatic graft versus host disease; however, these procedures are rarely performed because of procedural bleeding risk.

Adult SOS/VOD diagnosis

The 2023 EBMT diagnostic criteria[3] have some overlap with the Modified Seattle and Baltimore criteria; however, the main difference is the use of hyperbilirubinaemia for diagnosis. The EBMT criteria allow adult patients to meet two of the following criteria for a 'probable' SOS/VOD diagnosis: bilirubin ≥2 mg/dL (34.2 μmol/L), painful hepatomegaly, weight gain >5%, ascites, ultrasound and/or elastography suggestive of SOS/VOD (Table 1). This category is introduced in recognition that approximately 23% of HSCT patients with proven SOS/VOD have bilirubin levels at <2 mg/dL at diagnosis and would thus potentially be denied early defibrotide therapy.[11] The EBMT clinical diagnosis criteria are the same as the probable diagnosis criteria; however, bilirubin must be elevated (≥2 mg/dL) for a clinical diagnosis.[3] Proven SOS/VOD requires histological or haemodynamic (HVPG ≥10 mmHg) confirmation.[3]

Paediatric SOS/VOD diagnosis

SOS/VOD incidence in children is approximately double that of adults (20% vs 10%).[4] There are notable differences in disease, incidence, presentation and outcomes

Table 1 European Society for Blood and Marrow Transplantation (EBMT) clinical diagnostic criteria for sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) in adults (probable diagnosis)[3] and children (clinical diagnosis)[4]

	Adults	Children
Presence of two or more of the following:		
Weight change	Weight gain >5%	Otherwise, unexplained weight gain on three consecutive days despite use of diuretics or a weight gain >5% above baseline value
Ascites	Ascites	Ascites (best if confirmed by imaging) above baseline value†
Bilirubin	Bilirubin ≥2 mg/dL (≥34 μmol/L)	Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥2 mg/dL (≥34 μmol/L) within 72 h
Hepatomegaly	Painful hepatomegaly	Hepatomegaly (best if confirmed by imaging) above baseline value†
Thrombocytopenia		Unexplained consumptive and transfusion-refractory thrombocytopenia (≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines)‡
Time of onset	No limitation for time of onset of SOS/VOD	No limitation for time of onset of SOS/VOD

†Suggested: imaging (ultrasonography, computed tomography or magnetic resonance imaging) immediately before haemopoietic cell transplantation to determine baseline value for both hepatomegaly and ascites.
‡≥1 Weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.

between adult and paediatric populations. Given that SOS/VOD often differs in clinical presentation between children and adults, the EBMT proposed new SOS/VOD diagnostic and severity criteria tailored to children[4] (Table 1). Transfusion-refractory thrombocytopenia is often the first sign of SOS/VOD and is now recognised as a highly sensitive early clinical marker in children and is defined by unexplained consumptive and transfusion-refractory thrombocytopenia (≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines) (Table 1). Weight gain on three consecutive days in addition to refractoriness to diuretic treatment is also a diagnostic criterion; this is unlike the Modified Seattle or Baltimore criteria, which recommend a weight gain over 2% or 5% as one sign of SOS/VOD (Table 1).[4] The EBMT paediatric criteria do not emphasise a predefined level of hyperbilirubinaemia in children but rather require a rise in bilirubin from the baseline level on three consecutive days.[4] Children are at risk of other HSCT complications (including thrombotic microangiopathy and graft vs host disease) which must be considered in the differential diagnosis of SOS/VOD. The two processes may occur concurrently, and therefore treatment of both disease processes is required.

Adolescent and young adult (AYA) SOS/VOD patients may present similarly to paediatric patients. Management of the AYA population is an area that may evolve with time.

SOS/VOD severity grading

According to the EBMT criteria, there are four severity gradings (mild, moderate, severe and very severe) for both adults and children (Table 2). In adults, these stages have been based on various parameters, including bilirubin level and kinetics, weight gain, renal function (creatinine), transaminase level and time since first clinical manifestation.[3] The EBMT severity criteria were validated in a group of 203 patients with SOS/VOD.[21]

Unlike the adult criteria, the paediatric EBMT severity criteria (Table 2) also consider liver function (alanine transaminases, aspartate transaminase and glutamate dehydrogenase), the presence of refractory thrombocytopenia, ascites, coagulation, glomerular filtration rate, pulmonary function (oxygen requirement) and central nervous system function.[4]

SOS/VOD prevention

All patients should undergo a comprehensive risk assessment which considers reversal of any modifiable risk factors where possible and the administration of pharmacoprophylaxis. Where possible, HSCT delay is recommended until major risk factors have been addressed. There is potential for increased SOS/VOD risk when using total body irradiation (TBI) or alkylating agents. As such, these increased risks should be considered when tailoring the patient's SOS/VOD prophylaxis strategy and should be discussed with the patient prior to treatment. Alternatives include the use of non-TBI-based conditioning or reduced-intensity conditioning, avoidance of hepatotoxins and the use of pharmacokinetic guided busulfan targeted dosing as conditioning.[22] Optimisation of liver function, where possible, and stipulation of a minimum acceptable level of liver function should be prioritised prior to HSCT.

The use of conditioning regimens containing dual alkylating agents after treatment with the antibody–drug conjugate InO has been associated with the development of SOS/VOD.[7] To prevent SOS/VOD, dual alkylating agents should be avoided if possible following InO

Table 2 European Society for Blood and Marrow Transplantation (EBMT) for grading the severity of suspected sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) in adults[3] and children[4]

	Adults†	Children‡
Bilirubin (mg/dL)§,¶		
Mild	≥2 and <3	<2
Moderate	≥3 and <5	<2
Severe	≥5 and <8	≥2
Very severe	≥8	≥2
Bilirubin (μmol/L)		
Mild	≥34 and <52	<34
Moderate	≥52 and <86	<34
Severe	≥86 and <137	≥34
Very severe	≥137	≥34
Bilirubin kinetics		
Mild	Doubling within 48 h	Doubling within 48 h
Moderate		
Severe		
Very severe		
Other LFT	(Transaminases)	(ALT, AST, GLDH)§
Mild	≤2 × normal	≤2 × normal
Moderate	>2 and ≤5 × normal	>2 and ≤5 × normal
Severe	>5 and ≤8 × normal	>5
Very severe	>8 × normal	>5
Renal function	(Creatininemia)	(GFR (mL/min))
Mild	Baseline at transplant	89–60
Moderate	<1.5 × baseline at transplant	59–30
Severe	≥1.5 and <2 × baseline at transplant	29–15
Very severe	≥2 × baseline at transplant or diagnosis of MOD	<15 (renal failure)
Weight increase		
Mild		
Moderate		
Severe	≥5%	
Very severe	≥10%	
Ascites§		
Mild		Minimal
Moderate		Moderate
Severe		Necessity for paracentesis (external drainage)
Very severe		Necessity for paracentesis (external drainage)
Persistent refractory thrombocytopenia§		
Mild		<3 days
Moderate		3–7 days
Severe		>7 days
Very severe		>7 days
Coagulation		
Mild		Normal
Moderate		Normal
Severe		Impaired coagulation
Very severe		Impaired coagulation
Pulmonary function (oxygen requirement)		
Mild		<2 L/min
Moderate		>2 L/min
Severe		Invasive pulmonary ventilation (including CPAP)
Very severe		Invasive pulmonary ventilation (including CPAP)
CNS		
Mild		Normal
Moderate		Normal
Severe		Normal
Very severe		New onset cognitive impairment

Table 2 *Continued*

	Adults†	Children‡
Time since clinical symptoms		
Mild	>7 days	
Moderate	5–7 days	
Severe	≤4 days	
Very severe	Any time	

†In adults: in case of presence of two or more mild or moderate risk factors for SOS/VOD, patients should be in the upper grade; patients with 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.

‡In children: if patient fulfils criteria in different categories, they must be classified in the most severe category. In addition, the kinetics of the evolution of cumulative symptoms within 48 h predicts severe disease.

§In children: presence of ≥2 of these criteria qualifies for an upgrade to CTCAE level 4 (very severe SOS/VOD).

¶In children: excluding pre-existent hyperbilirubinaemia because of primary disease.

ALT, alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; CPAP, continuous positive airway pressure; GFR, glomerular filtration rate; GLDH, glutamate dehydrogenase; LFT, liver function test; MOD, multiorgan dysfunction; SOFA, Sequential Organ Failure Assessment.

therapy. In some patients, a similar effectiveness of salvage prior to transplant could be achieved with alternative agents, and such agents should be considered.

A key consideration in the context of InO and GO is the total prior doses or recency of HSCT commencement to the last dose. If HSCT is being planned, we recommend a maximum of two cycles (six doses) InO followed by at least 6 weeks without InO prior to HSCT commencement. For GO, we recommend a washout of 12 weeks after the last GO dose before HSCT commencement. Concurrent use of potential hepatotoxic agents, such as azole antifungals, should be closely monitored for toxicity and/or avoided where possible. Avoidance of particular HSCT conditioning regimens (e.g. dual alkylator and TBI-containing) may also be prudent, as well as extended ursodeoxycholic acid (UDCA) prophylaxis both pre- and post-HSCT.

Another important consideration is the use of therapeutic drug monitoring (TDM) for SOS/VOD-promoting agents, particularly busulfan, where SOS/VOD risk is increased among those with elevated AUC levels. SOS/VOD risk may be ameliorated if optimal dosing of these agents is delivered.

Currently, pharmacologic options for SOS/VOD prophylaxis are limited; they include UDCA and defibrotide. Although heparin was previously used on the basis that blood clot prevention may prevent SOS/VOD, subsequent understanding of disease biology suggests that this strategy is unlikely to be helpful; this is supported by multiple analyses failing to show any conclusive evidence that heparin prevents SOS/VOD.[22,23] Heparin also poses challenges in terms of bleeding risk for thrombocytopenic HSCT patients.

UDCA appears efficacious in preventing SOS/VOD[3,13]; a systematic review of three randomised studies demonstrated that UDCA reduced the risk of SOS/VOD relative to no treatment (relative risk = 0.34; 95% CI = 0.17–0.66).[24] Furthermore, a prospective randomised study of 242 patients found that UDCA maintained favourable overall survival (OS) and non-relapse mortality (NRM) rates at 10-year follow-up compared to no treatment (OS = 48% vs 38%, $P = 0.037$; NRM = 28% vs 41%, $P = 0.01$).[25] The EBMT recommends UDCA prophylaxis commencing prior to conditioning and continuing until day +90 after HSCT for both adults and children.[3,13]

The benefit, if any, of defibrotide prophylaxis is less clear. Although several studies reported reduced SOS/VOD incidence,[26–28] the recent HARMONY trial, a prospective randomised phase III trial of defibrotide SOS/VOD prophylaxis in 372 high-risk paediatric and adult HSCT recipients, failed to demonstrate a significant reduction in SOS/VOD incidence using the predefined primary end-point of SOS/VOD-free survival at day 30 after HSCT (67% vs 73% respectively, $P = 0.85$).[29] An earlier prospective randomised trial, the Paediatric Prevention trial, did demonstrate a reduction in the incidence of SOS/VOD from 20% to 12% ($P = 0.049$) in a high-risk paediatric cohort.[30] The HARMONY trial design has been criticised because the sample size was determined based on an assumed SOS/VOD incidence of 28% in the control arm; this unrealistic assumption likely resulted in insufficient study power to detect a significant difference. Other methodological concerns with the trial included the use of SOS/VOD-free survival by day 30 as the primary end-point which does not take into consideration the reduction in morbidity (as opposed to mortality) achieved by the intervention or the impact of allowing defibrotide use for the treatment of emergent SOS/VOD in the control group.[31] In summary, there is evidence of benefit of prophylactic defibrotide in a high-risk paediatric cohort, but this was not replicated in the HARMONY trial. However, methodological flaws make this trial difficult to interpret, and the value of prophylactic defibrotide should still be considered an unanswered question.

Management of established SOS/VOD

In Australia and New Zealand, SOS/VOD treatment strategies include supportive care and defibrotide, as well as high-dose methylprednisolone in paediatrics.[32] Extensive supportive care measures are essential in the management of SOS/VOD, potentially more so than specific therapeutic agents, and may ameliorate the severity of established SOS/VOD and improve patient outcomes.[33] Recommended supportive care includes analgesia, avoidance of hepatotoxins and nephrotoxins, respiratory support and drainage of ascites and pleural effusions.[22] Aggressive optimisation of volume status is paramount, including diuretics, salt/water restriction and/or dialysis. Specialist hepatology units should be consulted early for the management of severe SOS/VOD; the need for a transjugular intrahepatic portosystemic shunt should also be considered.[22]

Defibrotide (25 mg/kg/day for at least 14–21 days and until resolution of all SOS/VOD symptoms) is standard treatment for SOS/VOD in both adults and children.[13] A multicentre phase III trial assessing the effect of defibrotide in 102 patients with severe SOS/VOD found that defibrotide treatment was associated with greater survival at day +100 after HSCT compared to historical controls (38.2% vs 25%; 95.1% CI = 5.2–40.8, $P = 0.0109$). Furthermore, day +100 complete response rates were double (25.5% for defibrotide and 12.5% for controls; 95.1% CI = 3.5–34.6, $P = 0.0160$).[26]

In Australia, defibrotide is approved by the Therapeutic Goods Administration for the treatment of severe hepatic SOS/VOD; however, the EBMT criteria recommend its use in patients as early as moderate SOS/VOD.[3] This is because even moderate SOS/VOD is associated with significant mortality, and defibrotide is associated with higher day +100 survival.[34] In New Zealand, defibrotide is approved by Pharmac on the Hospital medicines list for use in moderate and severe SOS/VOD. Currently, there is observed variability in treatment and dosing approaches for SOS/VOD between adult and paediatric centres.[10] Access to defibrotide in Australia is more restricted for adult patients than for paediatric patients. Further studies are required to establish the utility of early use of defibrotide for patients with moderate SOS/VOD given the poor outcomes seen in patients with severe SOS/VOD.[10]

Practical aspects specific to Australian/New Zealand healthcare setting

There is significant variability in the pharmacologic management of SOS/VOD between Australian/New Zealand adult and paediatric centres. The dose of defibrotide (25 mg/kg/day) is well established and is recommended by the EBMT for at least 14–21 days and until the resolution of all SOS/VOD symptoms.[3] A recent study found that, while the dose and duration of defibrotide administration were consistent across Australian paediatric centres, defibrotide administration was variable across adult centres.[10] Some centres utilise a shorter course of defibrotide (7 days) with re-evaluation of progress at that time point on the rationale that most patients will have demonstrated their response by that time point. There were significant differences in the median dose ($P = 0.04$) and in the median therapy duration ($P = 0.035$) across adult centres. Study authors noted that further investigation of the effect of this variability on clinical outcomes is needed.[10]

In Australia and New Zealand, defibrotide is used for severe cases since that is where the best evidence exists for its efficacy. In contrast, defibrotide use in paediatric centres is more prevalent. This difference in practice across adult and paediatric centres is potentially attributed to more stringent criteria used by adult centres, which historically have required a diagnosis of severe or more progressed SOS/VOD to initiate therapy with defibrotide.[10] Australian adult SOS/VOD patients who received defibrotide were found to have a significantly reduced OS rate compared to those who received supportive care only. The observation of this unfavourable outcome in adults can be explained by defibrotide being used predominantly in patients with the most severe or progressed SOS/VOD.[10] Earlier treatment with defibrotide has been shown to increase the chance of survival,[35] along with decreased overall healthcare costs.[36] Initiating the use of defibrotide at moderate/severe disease severity is recommended.

Recommendations

1 HSCT recipients should be prospectively assessed for potential SOS/VOD risk, with the application of risk-modification strategies where feasible.
2 All HSCT recipients receive UDCA prophylaxis from conditioning commencement to day + 90 after HSCT.
3 SOS/VOD diagnosis/severity should be established, where possible, with reference to EBMT criteria.
4 In addition to best supportive care, SOS/VOD treatment should include defibrotide 25 mg/kg/day for 14–21 days in patients with moderate or severe disease, with weaning after response and cessation at SOS/VOD resolution.

Conclusion

Although our understanding of SOS/VOD biology has advanced in recent years, more work is required to

inform the development of improved prevention and treatment strategies. At present, SOS/VOD prevention is the most effective strategy, not only in terms of HSCT conditioning regimen selection and best standard of care during HSCT, but also HSCT timing in the context of the increasing pre-HSCT use of SOS/VOD-associated agents such as InO and GO. Treatment of SOS/VOD remains challenging, particularly in severe cases, many of which are fatal despite DFO treatment. Nevertheless, in the context of updated SOS/VOD diagnostic/severity criteria and the absence of other efficacious therapies, further work in the earlier detection of SOS/VOD and addressing the utility of DFO in earlier stages of severity may be helpful in improving these outcomes. There is an increasing need for validated biomarkers to identify patients at risk of SOS/VOD shortly after HSCT. Further research is required to develop new prophylactic and therapeutic options for SOS/VOD.

Acknowledgements

The authors thank Dulama Richani, PhD CMPP, of WriteSource Medical Pty Ltd., Sydney, Australia, for providing medical writing support by preparing the manuscript outline, developing the first draft and collating and incorporating author comments. Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

References

1 Carreras E. Veno-occlusive disease of the liver after hemopoietic cell transplantation. *Eur J Haematol* 2000; **64**: 281–91.
2 Bonifazi F, Barbato F, Ravaioli F, Sessa M, Defrancesco I, Arpinati M *et al*. Diagnosis and treatment of VOD/SOS after allogeneic hematopoietic stem cell transplantation. *Front Immunol* 2020; **11**: 489.
3 Mohty M, Malard F, Alaskar AS, Aljurf M, Arat M, Bader P *et al*. 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). *Bone Marrow Transplant* 2023; **58**: 749–54.
4 Corbacioglu S, Carreras E, Ansari M, Balduzzi A, Cesaro S, Dalle JH *et al*. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation. *Bone Marrow Transplant* 2018; **53**: 138–45.
5 Fujishima N, Uchida T, Onishi Y, Jung CW, Goh YT, Ando K *et al*. Inotuzumab ozogamicin versus standard of care in Asian patients with relapsed/refractory acute lymphoblastic leukemia. *Int J Hematol* 2019; **110**: 709–22.
6 Wadleigh M, Richardson PG, Zahrieh D, Lee SJ, Cutler C, Ho V *et al*. Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. *Blood* 2003; **102**: 1578–82.
7 Kantarjian HM, DeAngelo DJ, Advani AS, Stelljes M, Kebriaei P, Cassaday RD *et al*. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. *Lancet Haematol* 2017; **4**: e387–98.
8 Kebriaei P, Wilhelm K, Ravandi F, Brandt M, de Lima M, Ciurea S *et al*. Feasibility of allografting in patients with advanced acute lymphoblastic leukemia after salvage therapy with inotuzumab ozogamicin. *Clin Lymphoma Myeloma Leuk* 2013; **13**: 296–301.
9 Marks DI, Kebriaei P, Stelljes M, Gökbuget N, Kantarjian H, Advani AS *et al*. Outcomes of allogeneic stem cell transplantation after inotuzumab ozogamicin treatment for relapsed or refractory acute lymphoblastic leukemia. *Biol Blood Marrow Transplant* 2019; **25**: 1720–9.
10 Coutsouvelis J, Kirkpatrick CM, Dooley M, Spencer A, Kennedy G, Chau M *et al*. Incidence of sinusoidal obstruction syndrome/veno-occlusive disease and treatment with defibrotide in allogeneic transplantation: a multicenter Australasian registry study. *Transplant Cell Ther* 2023; **29**: 383.e1–383.e10.
11 Corbacioglu S, Kernan NA, Pagliuca A, Ryan RJ, Tappe W, Richardson PG. Incidence of anicteric Veno-occlusive disease/sinusoidal obstruction syndrome and outcomes with defibrotide following hematopoietic cell transplantation in adult and pediatric patients. *Biol Blood Marrow Transplant* 2020; **26**: 1342–9.
12 Szmit Z, Gorczynska E, Król A, Ussowicz M, Mielcarek-Siedziuk M, Olejnik I *et al*. Introduction of new pediatric EBMT criteria for VOD diagnosis: is it time-saving or money-wasting?: prospective evaluation of pediatric EBMT criteria for VOD. *Bone Marrow Transplant* 2020; **55**: 2138–46.
13 Mohty M, Malard F, Abecasis M, Aerts E, Alaskar AS, Aljurf M *et al*. Prophylactic, preemptive, and curative treatment for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a position statement from an international expert group. *Bone Marrow Transplant* 2020; **55**: 485–95.
14 McKoy JM, Angelotta C, Bennett CL, Tallman MS, Wadleigh M, Evens AM *et al*. Gemtuzumab ozogamicin-associated sinusoidal obstructive syndrome (SOS): an overview from the research on adverse drug events and reports (RADAR) project. *Leuk Res* 2007; **31**: 599–604.
15 Lambert J, Pautas C, Terré C, Raffoux E, Turlure P, Caillot D *et al*. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. *Haematologica* 2019; **104**: 113–9.
16 Battipaglia G, Labopin M, Candoni A, Fanin R, el Cheikh J, Blaise D *et al*. Risk of sinusoidal obstruction syndrome in allogeneic stem cell transplantation after prior gemtuzumab ozogamicin treatment: a retrospective study from the Acute Leukemia Working Party of

the EBMT. *Bone Marrow Transplant* 2017; **52**: 592–9.
17 McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology* 1984; **4**: 116–22.
18 Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG *et al*. Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation* 1987; **44**: 778–83.
19 Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M *et al*. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2016; **51**: 906–12.
20 Ravaioli F, Colecchia A, Alemanni LV, Vestito A, Dajti E, Marasco G *et al*. Role of imaging techniques in liver veno-occlusive disease diagnosis: recent advances and literature review. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 463–84.
21 Yoon J-H, Yoo KH, Sung KW, Jung CW, Kim JS, Hahn SM *et al*. Validation of treatment outcomes according to revised severity criteria from European Society for Blood and Marrow Transplantation (EBMT) for sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD). *Bone Marrow Transplant* 2019; **54**: 1361–8.
22 eviQ. Sinusoidal Obstruction Syndrome (SOS/VOD) Associated with Blood and Marrow Transplantation (BMT) (ID: 865 v.5); 2020 [26 July 2023]; Available from URL: https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/haematological/865-sinusoidal-obstruction-syndrome-sos-vod-asso#management.
23 Imran H, Tleyjeh IM, Zirakzadeh A, Rodriguez V, Khan SP. Use of prophylactic anticoagulation and the risk of hepatic veno-occlusive disease in patients undergoing hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Bone Marrow Transplant* 2006; **37**: 677–86.
24 Tay J, Tinmouth A, Fergusson D, Huebsch L, Allan DS. Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2007; **13**: 206–17.
25 Ruutu T, Juvonen E, Remberger M, Remes K, Volin L, Mattsson J *et al*. Improved survival with ursodeoxycholic acid prophylaxis in allogeneic stem cell transplantation: long-term follow-up of a randomized study. *Biol Blood Marrow Transplant* 2014; **20**: 135–8.
26 Richardson PG, Riches ML, Kernan NA, Brochstein JA, Mineishi S, Termuhlen AM *et al*. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood* 2016; **127**: 1656–65.
27 Cheuk DK, Chiang AKS, Ha SY, Chan GCF, Cochrane Haematological Malignancies Group. Interventions for prophylaxis of hepatic veno-occlusive disease in people undergoing haematopoietic stem cell transplantation. *Cochrane Database Syst Rev* 2015; **2015**: Cd009311.
28 Dalle JH, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. *Biol Blood Marrow Transplant* 2016; **22**: 400–9.
29 Grupp SA, Corbacioglu S, Kang HJ, Teshima T, Khaw SL, Locatelli F *et al*. Defibrotide plus best standard of care compared with best standard of care alone for the prevention of sinusoidal obstruction syndrome (HARMONY): a randomised, multicentre, phase 3 trial. *Lancet Haematol* 2023; **10**: e333–45.
30 Corbacioglu S, Cesaro S, Faraci M, Valteau-Couanet D, Gruhn B, Rovelli A *et al*. Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet* 2012; **379**: 1301–9.
31 Corbacioglu S, Grupp SA, Richardson PG, Duarte R, Pagliuca A, Ruutu T *et al*. Prevention of veno-occlusive disease/sinusoidal obstruction syndrome: a never-ending story and no easy answer. *Bone Marrow Transplant* 2023; **58**: 839–41.
32 Gloude NJ, Jodele S, Teusink-Cross A, Grimley M, Davies SM, Lane A *et al*. Combination of high-dose methylprednisolone and defibrotide for veno-occlusive disease in pediatric hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2018; **24**: 91–5.
33 Rayner P, Spruit JL, Chu R, Yankelevich M, Henry M, Ravindranath Y *et al*. Role of initiating supportive care preceding veno-occlusive disease diagnosis following allogeneic hematopoietic stem cell transplantation in children. *J Pediatr Hematol Oncol* 2019; **41**: e395–401.
34 Kernan NA, Grupp S, Smith AR, Arai S, Triplett B, Antin JH *et al*. Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Br J Haematol* 2018; **181**: 816–27.
35 Richardson PG, Smith AR, Triplett BM, Kernan NA, Grupp SA, Antin JH *et al*. Earlier defibrotide initiation post-diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome improves day +100 survival following haematopoietic stem cell transplantation. *Br J Haematol* 2017; **178**: 112–8.
36 Carcedo Rodriguez D, Artola Urain T, Chinea Rodriguez A, García Torres E, González Vicent M, Gutiérrez García G *et al*. Cost-effectiveness analysis of defibrotide in the treatment of patients with severe veno-occlusive disease/sinusoidal obstructive syndrome with multiorgan dysfunction following hematopoietic cell transplantation in Spain. *J Med Econ* 2021; **24**: 628–636.