Today's evolving
HSCT landscape requires...

READINESS.
RECOGNITION.
REACTION.

Increased vigilance is key to identifying VOD

A potentially life-threatening and rapidly progressing complication[1-3]:

VOD

A post-HSCT complication primarily associated with conditioning regimens that affects the endothelial cells within the sinusoids of the liver[1,4]

RAPIDLY PROGRESSIVE

Approximately
30% to 50%
of cases developed multi-organ dysfunction[2,a]

DEADLY

84%
overall mortality in VOD with multi-organ dysfunction[1,b]

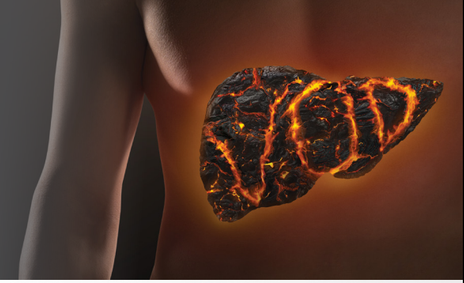
[a]Based on a study conducted by Carreras et al that used 2 sets of diagnostic criteria to estimate the incidence of VOD after HSCT.

[b]Based on 19 studies from a meta-analysis of 135 studies.

HSCT=hematopoietic stem-cell transplantation; VOD=veno-occlusive disease (also known as sinusoidal obstruction syndrome, or SOS).

VOD is a complex cascade of events that

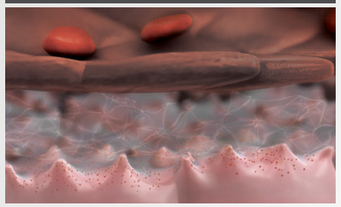
CAN ULTIMATELY LEAD TO DEATH[1-3,5-14]



VOD is a post-HSCT complication thought to be a consequence of conditioning regimen–induced damage to sinusoidal endothelial cells[5-7]

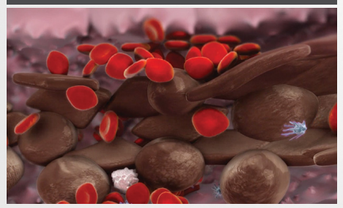
Buildup of toxic metabolites from the conditioning regimen[5-7]

Endothelial cell damage[5-7]



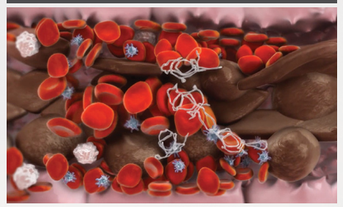
- Expression of cytokines and adhesion molecules is triggered by endothelial cell activation
- Activation of inflammatory pathways causes additional endothelial damage
- Extracellular matrix degradation and disruption of cytoskeletal structure lead to the formation of gaps in the endothelium

Sinusoidal narrowing[5-7]



- Red blood cells, leukocytes, and cellular debris accumulate in the space of Disse
- Endothelial cells dissect and embolize downstream

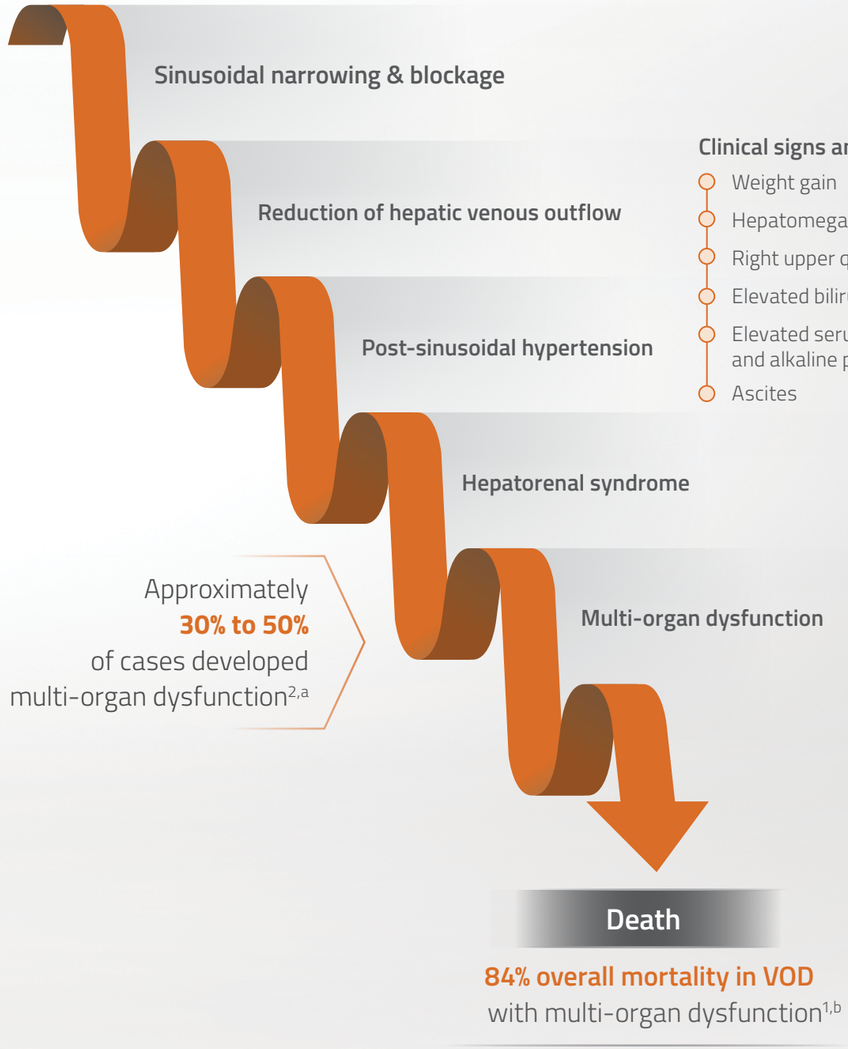
Sinusoidal blockage[1,6-10]



- Expression of factors that regulate coagulation and fibrinolysis contributes to a prothrombotic and hypofibrinolytic state
- Fibrin deposition, clot formation, and sinusoidal narrowing lead to further sinusoidal obstruction
- Hepatocyte cell death may occur

The cascade of events appears to start **before** clear pathological and clinical manifestations are evident[6,7]

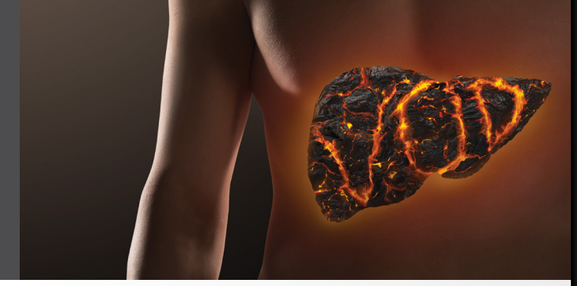
VOD can progress from endothelial cell damage to multi-organ dysfunction and death[1-3,5-14]



[a]Based on a study conducted by Carreras et al that used 2 sets of diagnostic criteria to estimate the incidence of VOD after HSCT.
[b]Based on 19 studies from a meta-analysis of 135 studies.

Know the multiple factors that can impact the

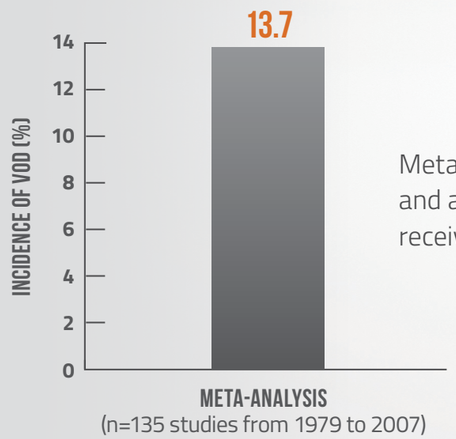
INCIDENCE OF VOD



Historically, factors that may impact incidence include[1,2,15,16]:

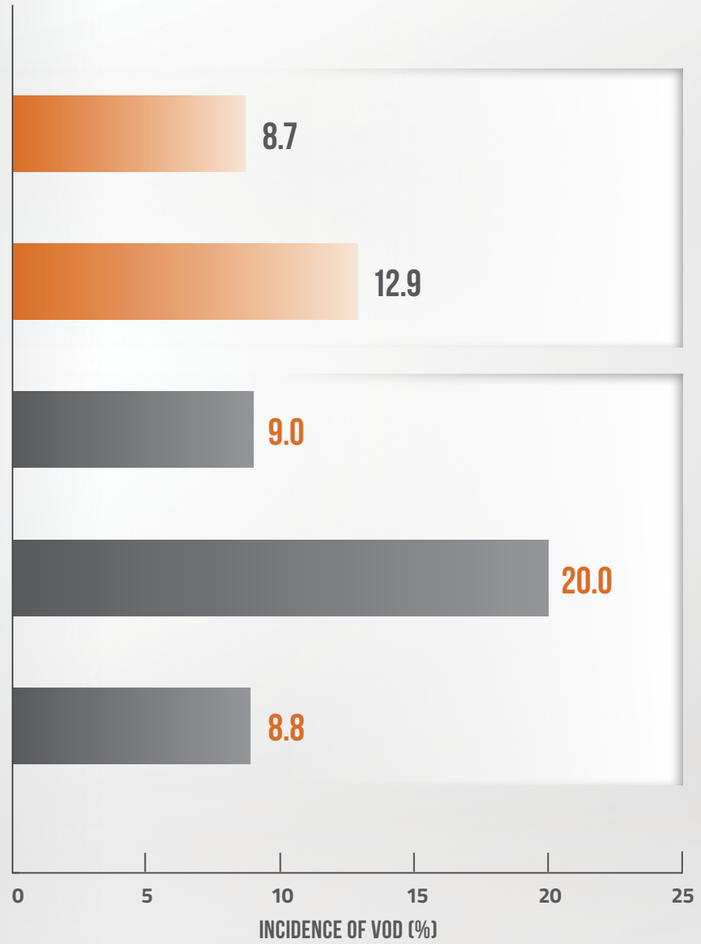
- CONDITIONING REGIMEN
- TYPE OF TRANSPLANT
- UNDERLYING DISEASE
- DIAGNOSTIC CRITERIA USED

Incidence of VOD based on a meta-analysis[1]



Meta-analysis included both allogeneic and autologous stem-cell transplant patients receiving either RIC or MAC regimens

Incidence of VOD based on the type of transplant and conditioning regimen



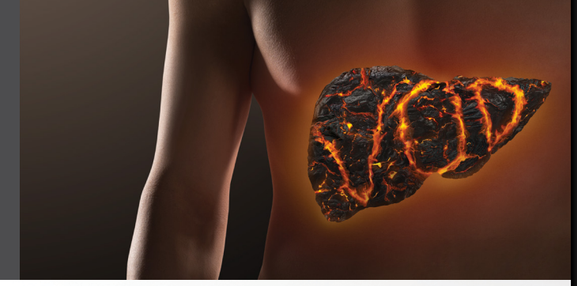
Reduced-intensity conditioning does not eliminate the risk of VOD, as many other factors can put patients at risk[11,15,19]

MAC=myeloablative conditioning; RIC=reduced-intensity conditioning.

[a]Moderate-to-severe VOD.

Be ready by identifying preexisting

RISK FACTORS FOR VOD



Most patient-related, disease-related, and hepatic-related risk factors are typically non-modifiable[19]

Patient- and disease-related risk factors[11,19]

- Female receiving norethisterone
- Older age (in adult patients)
- Karnofsky score <90%
- Genetic factors (*GSTM1* polymorphism, *C282Y* allele, *MTHFR 677CC/1298CC* haplotype)
- Thalassemia
- Adult metabolic syndrome
- Advanced disease (beyond second CR or relapse/refractory)
- Deficit of AT III or t-PA
- Resistance to activated protein C

Hepatic-related risk factors[11,19]

- **Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin**
- Transaminase levels >2.5 x ULN
- Serum bilirubin >1.5 x ULN
- Cirrhosis
- Hepatic fibrosis
- Active viral hepatitis
- Abdominal or hepatic irradiation
- Use of hepatotoxic drugs
- Iron overload

Transplant-related risk factors are modifiable[19]

Transplant-related risk factors[11,19]

- Allogeneic HSCT
- Second HSCT
- Myeloablative conditioning regimen
- Non–T-cell-depleted graft
- Unrelated donor/HLA mismatch
- Oral or high-dose BU-based conditioning regimen
- High-dose TBI-based conditioning regimen

Vigilant monitoring is important regardless of risk factors, as VOD can occur in any patient following HSCT

With a higher incidence of VOD in children, it is critical to recognize risk factors specific to this vulnerable patient population[12,19]

Pediatric-specific risk factors

- Low weight[19]
- Age <2 years[12,19]
- Lansky score <90[2,20]
- History of any of the following diseases[12,19]:
  - Hemophagocytic lymphohistiocytosis
  - Adrenoleukodystrophy
  - Osteopetrosis
  - High-dose auto-HSCT for neuroblastoma
  - Juvenile myelomonocytic chronic leukemia
  - Hemoglobinopathies
    - Sickle cell disease
    - Thalassemia

Overall incidence of VOD in children and infants is ~20%[12,a]

This is 2-fold higher than in adults[17,18]

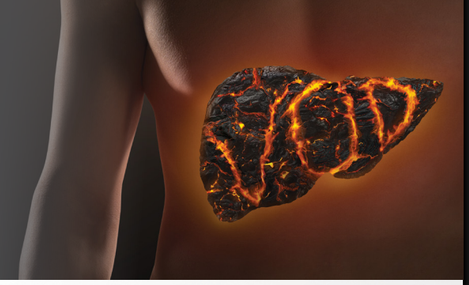
Incidence can be up to 60% in high-risk patients[12,a]

[a]Based on a position paper proposing diagnostic and severity criteria for SOS/VOD in pediatric patients on behalf of the European Society for Blood and Marrow Transplantation (EBMT).

AT=antithrombin; BU=busulfan; CR=complete remission; HLA=human leukocyte antigen; TBI=total body irradiation; t-PA=tissue plasminogen activator; ULN=upper limit of normal.

Multiple diagnostic criteria have been utilized to

RECOGNIZE AND DIAGNOSE VOD



Historically, 2 different criteria have been used for VOD diagnosis[5]

Modified Seattle criteria

Presentation before Day 20 post HSCT of at least 2 of the following:

- Bilirubin >2 mg/dL
- Hepatomegaly or right upper quadrant pain
- Weight gain (>2%)

Baltimore criteria

Presentation of bilirubin >2 mg/dL before Day 21 post HSCT and at least 2 of the following:

- Painful hepatomegaly
- Ascites
- Weight gain (>5%)

Limitations of current diagnostic criteria[11,12,19]

- Signs and symptoms of VOD can occur after the first 21 days post HSCT
- VOD that presents in the absence of specified signs and symptoms, such as hyperbilirubinemia, is not considered
- Differing clinical presentation between adults and children

Early signs suggestive of VOD include **increased need for platelet transfusion and fluid retention causing weight gain[21]**

EBMT has proposed new criteria for diagnosing VOD in adults and children

Revised EBMT criteria for adults[11]

VOD that occurs ≤21 days post HSCT:

Baltimore criteria[a]

Late onset VOD >21 days post HSCT:

Baltimore criteria[a] beyond Day 21

OR histologically proven VOD

OR 2 or more of the following criteria must be present:

- Bilirubin ≥2 mg/dL (or 34 µmol/L)
- Painful hepatomegaly
- Weight gain >5%
- Ascites

AND hemodynamic or/and ultrasound evidence of VOD (hepatomegaly, ascites, and decrease in velocity or reversal of portal flow)

Revised EBMT criteria for children[12]

No limitation for time of onset of VOD

The presence of 2 or more of the following is required[b]:

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

Proposed EBMT criteria have not been prospectively validated in clinical trials

[a]Defined as classical VOD in EBMT criteria.

[b]With the exclusion of other potential differential diagnoses.

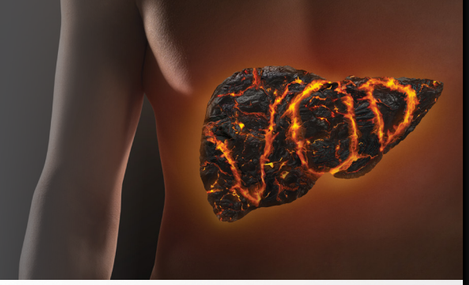
[c]≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.

[d]Suggested: imaging (US, CT, or MRI) immediately before HCT to determine baseline value for both hepatomegaly and ascites.

CT=computed tomography; EBMT=European Society for Blood and Marrow Transplantation; HCT=hematopoietic cell transplantation; MRI=magnetic resonance imaging; US=ultrasonography.

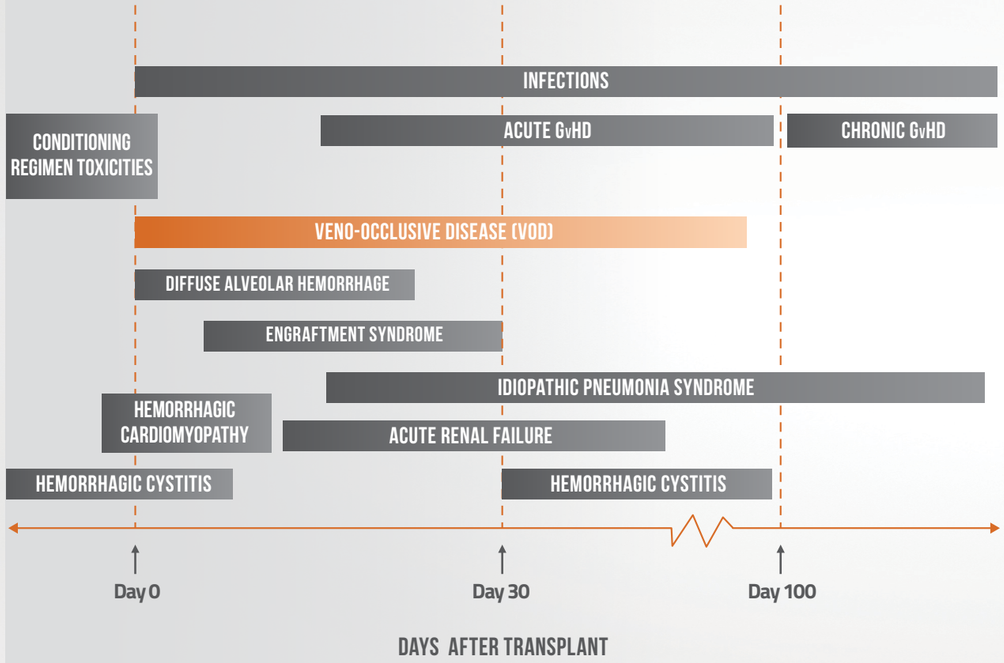
It is essential to consider VOD in the

DIFFERENTIAL DIAGNOSIS



Many complications can occur before and after HSCT, adding complexity to the differential diagnosis[22]

Pre- and post-HSCT complications



Note. Adapted and reprinted with permission of Oncology Nursing Society (ONS) from "Hematopoietic Stem Cell Transplantation: Implications for Critical Care Nurses" by M.G. Saria & T.K. Gosselin-Acomb, 2007, *Clinical Journal of Oncology Nursing*, 11(1), 57. Copyright © 2007 by ONS. All rights reserved.

VOD with multi-organ dysfunction is among the most **deadly post-HSCT complications**[1,23]

Several post-HSCT complications are characterized by signs and symptoms that overlap with those of VOD[5,12,24-26]

Rapid weight gain
- Congestive heart failure
- Renal failure
- Sepsis syndrome (cholangitis lenta)
- Capillary leak syndrome
- Iatrogenic fluid overload

Hepatomegaly
- Congestive heart failure
- Fungal infection
- Epstein-Barr virus lymphoproliferative disease
- Tumor involvement
- Myeloproliferative disorders

Jaundice
- Acute GvHD
- Biliary infection
- Calcineurin inhibitor toxicity
- Cholestasis
- Drug or total parenteral nutrition injury
- Hemolysis

It is important to keep VOD top of mind in the differential diagnosis, especially in patients with preexisting risk factors

Abdominal ultrasound can assist in the differential diagnosis of clinically suspected VOD

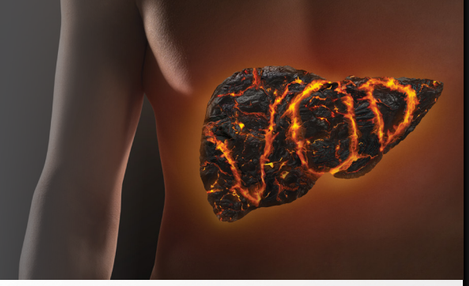
- **Baseline and serial ultrasound** measurements are recommended for **early VOD detection** and can also be used to confirm clinically suspected hepatomegaly and ascites[4,11,12]
- **Doppler** can be used to assess hepatic and portal vascular flow[11,12,21]
  – It is important to note that **lack of impairment of or reversal of portal vascular flow,** a late finding of VOD, **does not rule out a VOD diagnosis**

VOD is a **clinical diagnosis**

GvHD=graft-vs-host disease.

Be alert for signs of renal or pulmonary dysfunction

BE PREPARED TO ACT ON VOD



Signs and symptoms of multi-organ dysfunction may be predictive of VOD progression and poor survival[3,10]

Renal dysfunction may include[11,14,27,28]

- Decreased urinary output
- Elevated creatinine levels (≥1.5 x baseline)
- Decreased creatinine clearance
- Decreased glomerular filtration rate
- Need for dialysis

Pulmonary dysfunction may include[3,27,28]

- Pulmonary infiltrates
- Pleural effusion
- Reduced oxygen saturation
- Need for supplemental oxygen (nasal cannula)
- Ventilator dependence

Approximately **30% to 50%** of cases developed multi-organ dysfunction[2,a]

84% overall mortality in VOD with multi-organ dysfunction[1,b]

Signs of VOD progression[3,10-12]

Early onset

Signs and symptoms such as weight gain, hepatomegaly, and elevated bilirubin may appear early and worsen quickly post HSCT

Rapid worsening

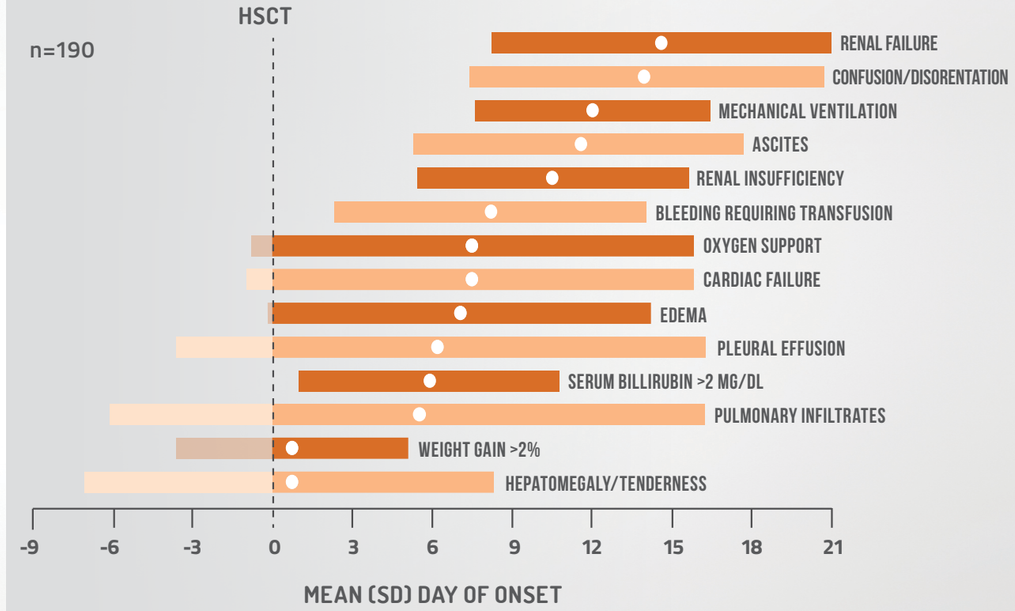
Short time from the first clinical symptoms to the date of VOD diagnosis

High magnitude of severity

Symptoms of severe liver dysfunction and extreme elevation in liver lab values

VOD can rapidly progress to renal or pulmonary dysfunction[3,4,10]

Average time of onset of symptoms in VOD post HSCT[3,10]

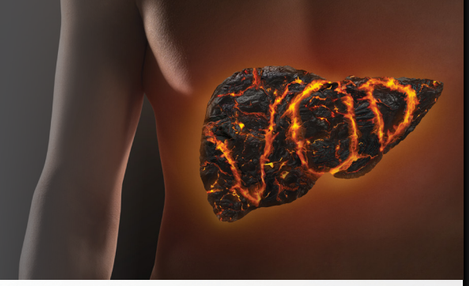


Study design: Time of onset of VOD and multi-organ failure is based on 190 patients from a prospective cohort evaluation of 355 consecutive patients. A diagnosis of VOD was made based on the occurrence of 2 of the following events within 20 days of transplantation: bilirubin >2 mg/dL, hepatomegaly or right upper quadrant pain of hepatic origin, and sudden weight gain (>2% of baseline weight). No other explanation for these signs and symptoms could be present at the time of diagnosis.[3,10]

[a]Based on a study conducted by Carreras et al that used 2 sets of diagnostic criteria to estimate the incidence of VOD after HSCT.
[b]Based on 19 studies from a meta-analysis of 135 studies.

Readiness and recognition are critical to immediate

VOD IDENTIFICATION



Vigilant monitoring for the first 21 days is critical to VOD detection[2,5,15]

Although VOD generally emerges within the first 21 days post HSCT, it can occur later[5,11,12]

Weight gain

- Is weight gain >2% above the baseline weight at the start of the conditioning regimen?

Edema and ascites

- Is edema present?
- Is abdominal distension/ascites present?
- Is patient experiencing shortness of breath?

Abdominal discomfort/pain

- Is patient experiencing abdominal discomfort/pain?
- Is pain localized to right upper quadrant?
- Is there liver tenderness?

Hepatomegaly

- Is hepatomegaly present?

Approximately **30% to 50%** of cases developed multi-organ dysfunction[2,a]

Jaundice

- Is bilirubin >2 mg/dL?

Liver function

- Are any liver function tests elevated?
  - Alkaline phosphatase
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
  - Gamma-glutamyl transpeptidase (GGT)

Fluid retention

- Is fluid retention present?

Renal function

- Has urinary output decreased?
- Is serum creatinine elevated relative to the start of conditioning regimen?
- Is glomerular filtration rate below normal?
- Does patient require dialysis?

Pulmonary function

- Does patient have blood oxygen saturation below normal?
- Does patient require oxygen support?
- Does patient require mechanical ventilation?

84% overall mortality in VOD with multi-organ dysfunction[1,b]

[a]Based on a study conducted by Carreras et al that used 2 sets of diagnostic criteria to estimate the incidence of VOD after HSCT.

[b]Based on 19 studies from a meta-analysis of 135 studies.

Increased vigilance is key to **IDENTIFYING VOD**

Approximately **30% to 50%** of cases developed multi-organ dysfunction[2,a]

84% overall mortality in VOD with multi-organ dysfunction[1,b]

[a]Based on a study conducted by Carreras et al that used 2 sets of diagnostic criteria to estimate the incidence of VOD after HSCT.

[b]Based on 19 studies from a meta-analysis of 135 studies.

References: **1.** Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant*. 2010;16(2):157-168. **2.** Carreras E, Díaz-Beyá M, Rosiñol L, et al. The incidence of veno-occlusive disease following allogeneic hematopoietic stem cell transplantation has diminished and the outcome improved over the last decade. *Biol Blood Marrow Transplant*. 2011;17(11):1713-1720. **3.** McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med*. 1993;118(4):255-267. **4.** Carreras E. How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. *Br J Haematol*. 2015;168(4):481-491. **5.** Carreras E. Early complications after HSCT. In: Apperley J, Carreras E, Gluckman E, et al, eds. *The EBMT Handbook*. 6th ed. Paris, France: European School of Haematology; 2012:176-195. **6.** Richardson PG, Ho VT, Cutler C, et al. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: novel insights to pathogenesis, current status of treatment, and future directions. *Biol Blood Marrow Transplant*. 2013;19(suppl 1):S88-S90. **7.** Richardson PG, Corbacioglu S, Ho VT, et al. *Exper Opin Drug Saf*. 2013;12(1):123-136. **8.** Vion AC, Rautou PE, Durand F, et al. Interplay of inflammation and endothelial dysfunction in bone marrow transplantation: focus on hepatic veno-occlusive disease. *Semin Thromb Hemost*. 2015;41(6):629-643. **9.** Coppell JA, Brown SA, Perry DJ. Veno-occlusive disease: cytokines, genetics, and haemostasis. *Blood Rev*. 2003;17(2):63-70. **10.** Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. *Blood*. 1995;85(11):3005-3020. 9. **11.** Mohty M, Malard F, Abecassis 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(7):906-912. **12.** Corbacioglu S, Carreras E, Ansari M, 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(2):138-145. **13.** Bayraktar UD, Seren S, Bayraktar Y. Hepatic venous outflow obstruction: three similar syndromes. *World J Gastroenterol*. 2007;13(13):1912-1927. **14.** Ng CK, Chan MH, Tai MH, et al. Hepatorenal syndrome. *Clin Biochem Rev*. 2007;28(1):11-17. **15.** Tsirigotis PD, Resnick IB, Avni B, et al. Incidence and risk factors for moderate-to-severe veno-occlusive disease of the liver after allogeneic stem cell transplantation using a reduced intensity conditioning regimen. *Bone Marrow Transplant*. 2014;49(11):1389-1392. **16.** Cheuk DK, Wang P, Lee TL, et al. Risk factors and mortality predictors of hepatic veno-occlusive disease after pediatric hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2007;40(10):935-944. **17.** Nagler A, Labopin M, Berger R, et al. Allogeneic hematopoietic SCT for adults AML using i.v. BU in the conditioning regimen: outcomes and risk factors for the occurrence of hepatic sinusoidal obstructive syndrome. *Bone Marrow Transplant*. 2014;49(5):628-633. **18.** Corbacioglu S, Cesaro E, Faraci M, et al. *Lancet*. 2012;379(9823):1301-1309. **19.** Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2015;50(6):781-789. **20.** Center for International Blood & Marrow Transplant Research. Appendix L: Karnofsky/Lansky performance status. https://www.cibmtr.org/manuals/fim/1/en/topic/appendix-l-karnofsky-lansky-performance-status. Accessed August 29, 2018. **21.** Bajwa RPS, Mahadeo KM, Taragin BH, et al. Consensus report by Pediatric Acute Lung Injury and Sepsis Investigators and Pediatric Blood and Marrow Transplantation Consortium Joint Working Committees: supportive care guidelines for management of veno-occlusive disease in children and adolescents, part 1: focus on investigations, prophylaxis, and specific treatment. *Biol Blood Marrow Transplant*. 2017;23(11):1817-1825. **22.** Saria MG, Gosselin-Acomb TK. Hematopoietic stem cell transplantation: implications for critical care nurses. *Clin J Oncol Nurs*. 2007;11(1):53-63. **23.** Gratwohl A, Hermans J, Apperly J, et al; Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Acute graft-versus-host disease: grade and outcome in patients with chronic myelogenous leukemia. *Blood*. 1995;86(2):813-818. **24.** Eisenberg S. Hepatic sinusoidal obstruction syndrome in patients undergoing hematopoietic stem cell transplant. *Oncol Nurs Forum*. 2008;35(3):385-397. **25.** Tuncer HH, Rana N, Milani C, et al. Gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *World J Gastroenterol*. 2012;18(16):1851-1860. **26.** Murakami J, Shimizu Y. Hepatic manifestations in hematological disorders. *Int J Hepatol*. 2013;2013:484903. **27.** Richardson PG, Murakami C, Jin Z, et al. *Blood*. 2002;100(13):4337-4343. **28.** Richardson PG, Riches ML, Kernan NA, et al. *Blood*. 2016;127(13):1656-1665.

Learn more at **PROGRESSIVEVOD**.com

Jazz Pharmaceuticals®