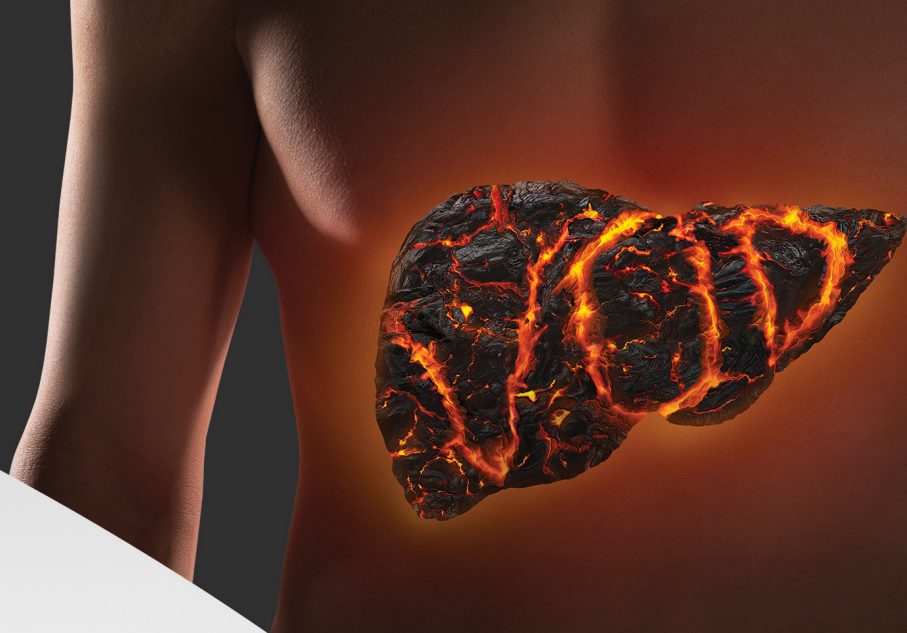




Today's evolving
HSCT landscape requires...

READINESS. RECOGNITION. REACTION.

Increased vigilance is key to identifying VOD

A potentially life-threatening and rapidly progressing complication¹⁻³:

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

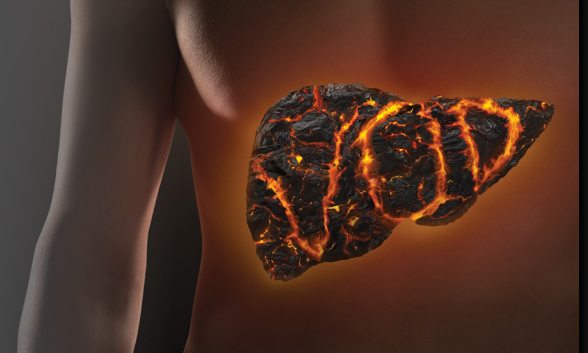
84%
overall mortality
in VOD with multi-organ
dysfunction^{1,b}

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

^bBased 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).

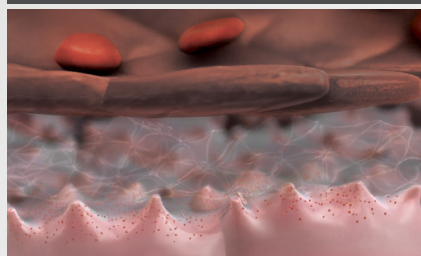
VOD is a complex cascade of events that CAN ULTIMATELY LEAD TO DEATH^{1-3,5-14}



- VOD is a post-HSCT complication thought to be a consequence of conditioning regimen–induced damage to sinusoidal endothelial cells⁵⁻⁷

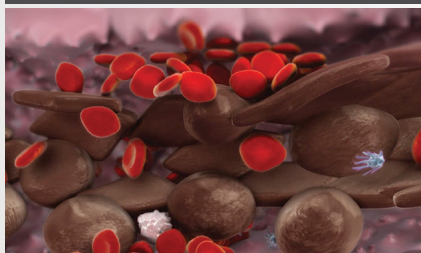
Buildup of toxic metabolites from the conditioning regimen⁵⁻⁷

Endothelial cell damage⁵⁻⁷



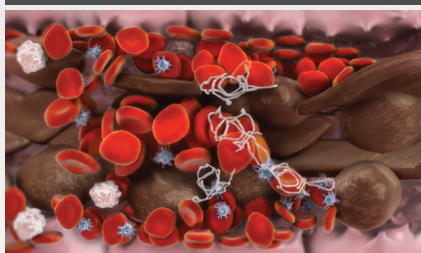
- Expression of cytokines and adhesion molecules is triggered by endothelial cell activation
- Activation of inflammatory pathways causes additional endothelial damage
- Extracellular matrix degradation and disruption of cytoskeletal structure lead to the formation of gaps in the endothelium

Sinusoidal narrowing⁵⁻⁷



- 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}

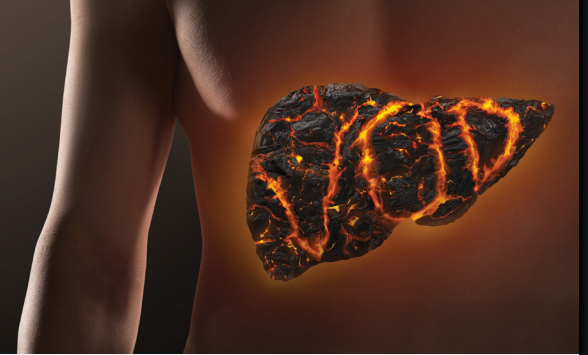
- VOD can progress from endothelial cell damage to multi-organ dysfunction and death^{1-3,5-14}



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

^bBased on 19 studies from a meta-analysis of 135 studies.

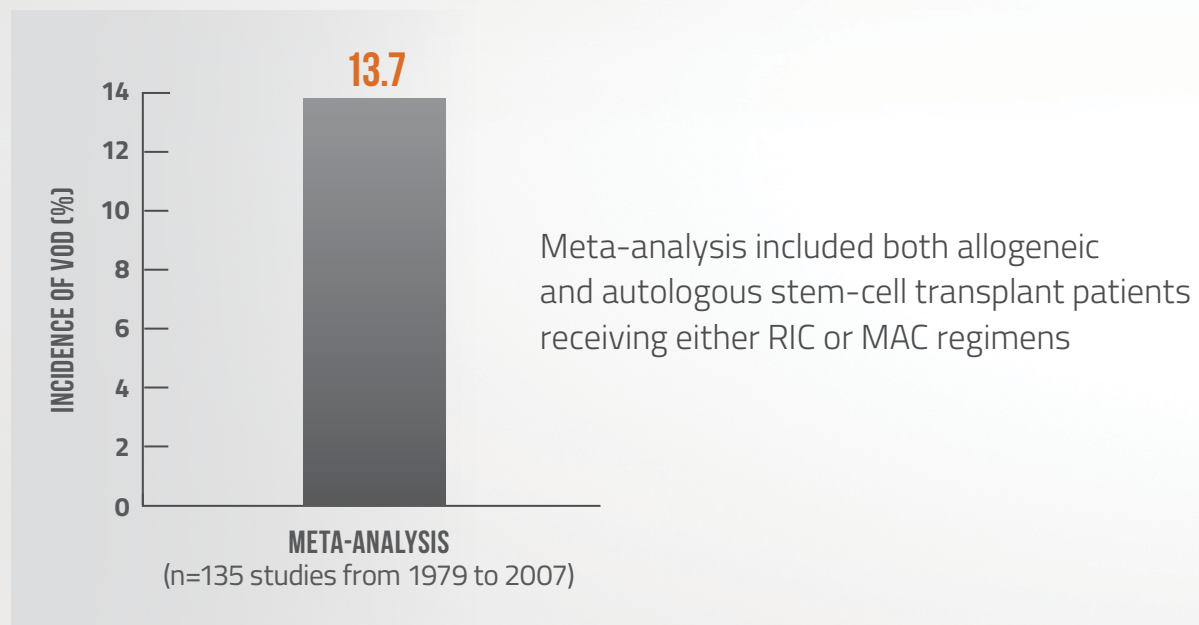
Know the multiple factors that can impact the INCIDENCE OF VOD



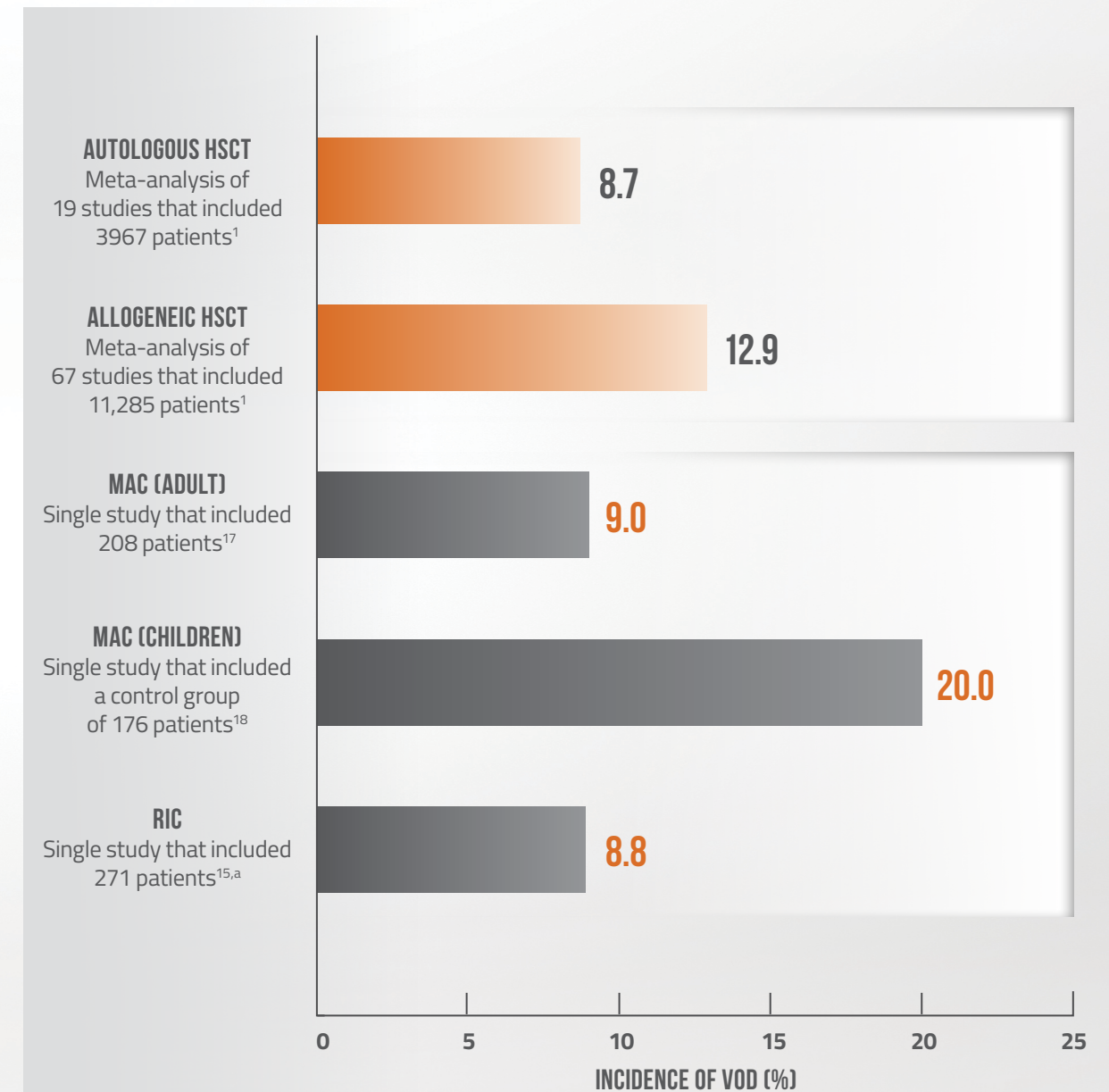
Historically, factors that may impact incidence include^{1,2,15,16}:



Incidence of VOD based on a meta-analysis¹



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}

Be ready by identifying preexisting RISK FACTORS FOR VOD



Most patient-related, disease-related, and hepatic-related risk factors are typically non-modifiable¹⁹



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 modifiable¹⁹



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 weight¹⁹
- 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}

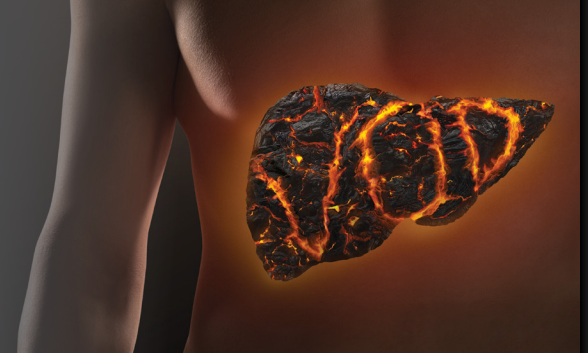
This is 2-fold higher than in adults^{17,18}

Incidence can be up to 60% in high-risk patients^{12,a}

^aBased 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 diagnosis⁵

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 gain²¹**

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

Revised EBMT criteria for adults¹¹

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

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

Revised EBMT criteria for children¹²

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

Proposed EBMT criteria have not been prospectively validated in clinical trials

^aDefined as classical VOD in EBMT criteria.

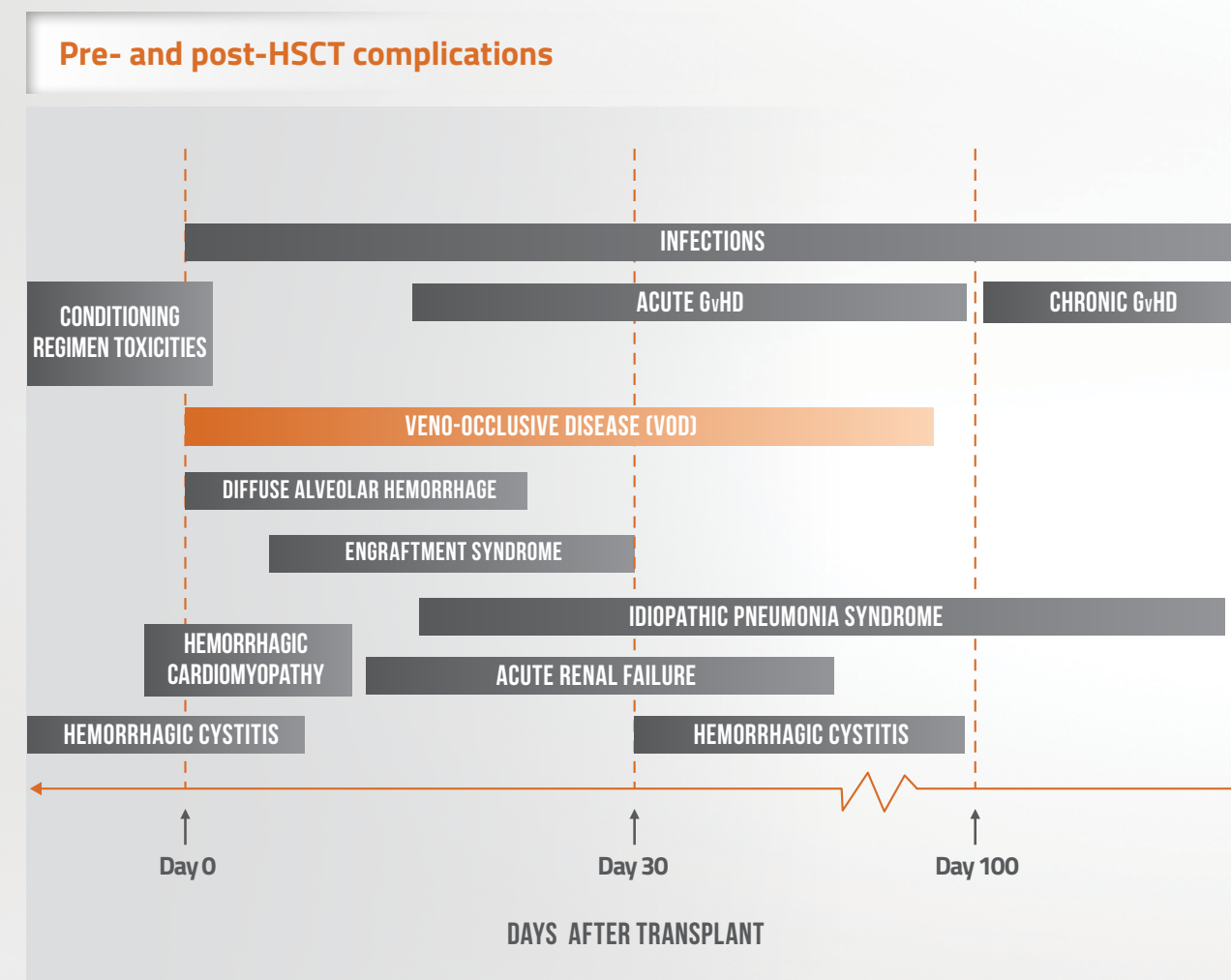
^bWith the exclusion of other potential differential diagnoses.

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

^dSuggested: 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 diagnosis²²



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	✓ Hepatomegaly	✓ Jaundice
○ Congestive heart failure ○ Renal failure ○ Sepsis syndrome (cholangitis lenta) ○ Capillary leak syndrome ○ Iatrogenic fluid overload	○ Congestive heart failure ○ Fungal infection ○ Epstein-Barr virus lymphoproliferative disease ○ Tumor involvement ○ Myeloproliferative disorders	○ 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

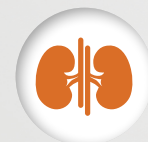
Abdominal ultrasound can assist in the differential diagnosis of clinically suspected VOD

- **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**

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 ($\geq 1.5 \times$ 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

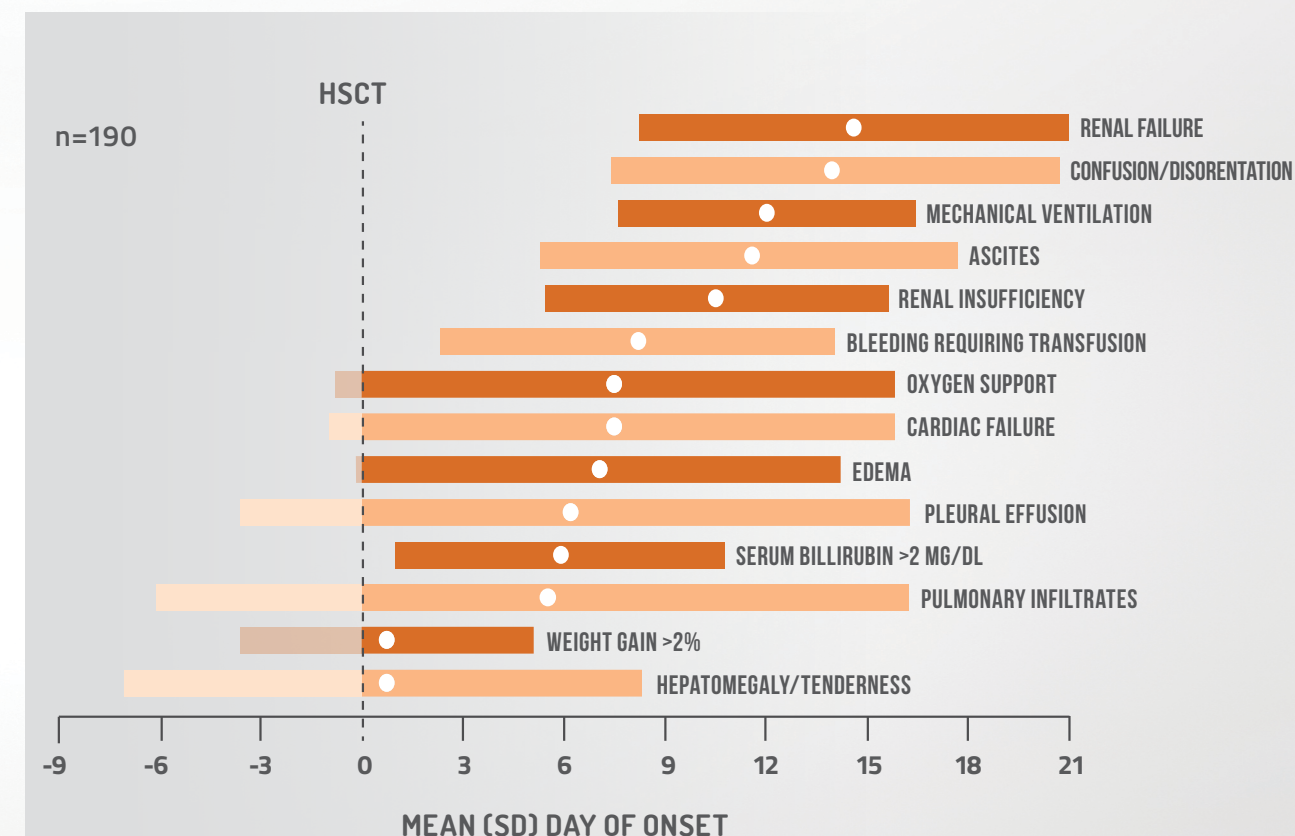
Short time from the first clinical symptoms to the date of VOD diagnosis

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}

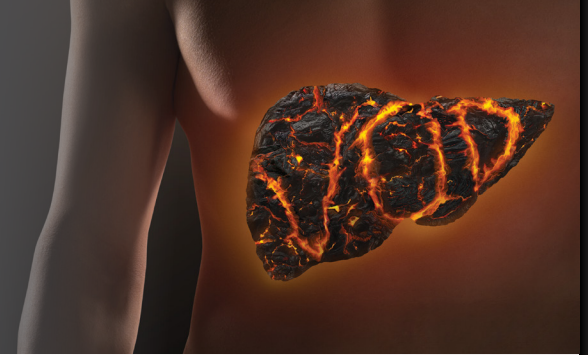


Study design: Time of onset of VOD and multi-organ failure is based on 190 patients from a prospective cohort evaluation of 355 consecutive patients. A diagnosis of VOD was made based on the occurrence of 2 of the following events within 20 days of transplantation: bilirubin >2 mg/dL, hepatomegaly or 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}

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

^bBased 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}

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}

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