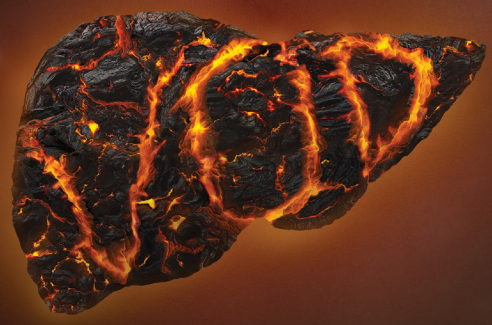
SEE THE SIGNS BEFORE VOD ERUPTS



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

KEY CONSIDERATIONS FOR PROMPT VOD DIAGNOSIS

START OF CONDITIONING REGIMEN

- ✓ **Monitor for signs and symptoms**
- ✓ **Assess for risk factors for VOD**
- DAY 0 HSCT
- ✓ **Consider VOD a part of differential diagnosis**
- DAY 21

VOD GENERALLY EMERGES WITHIN THE FIRST 21 DAYS POST HSCT[1-3]

CONSIDER PREEXISTING FACTORS THAT MAY INCREASE THE RISK FOR HEPATIC VOD[1,2,4-10]

Patient-related risk factors

- ✓ **Age**
  - Children under age 2
- ✓ **Preexisting hepatic disturbance or dysfunction**
  - Liver fibrosis
  - Previous liver disease
  - Elevated pre-HSCT AST/ALT
  - Hepatotoxic medication
  - Iron overload
- ✓ **Osteopetrosis (in children)**

Transplant-related risk factors

- ✓ **Allogeneic transplant**
- ✓ **HLA mismatch**
- ✓ **Previous myeloablative HSCT**
- ✓ **High-intensity conditioning regimens**
  - Oral busulfan
  - Busulfan, in combination with cyclophosphamide
- ✓ **Total body irradiation (high or single dose)**

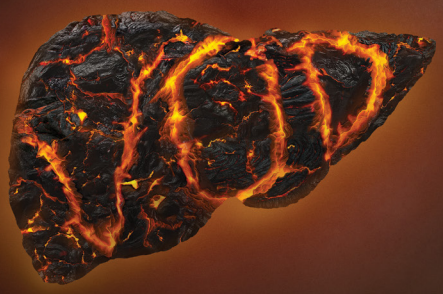
VOD MONITORING RECOMMENDATIONS IN POST-HSCT PATIENTS[7,11]

✓ **Begin VOD monitoring**	Start of the conditioning regimen
✓ **Length of monitoring**	Daily monitoring is recommended for 14 to 21 days post HSCT
✓ **Signs and symptoms to monitor**	▪ Weight gain ▪ Fluid retention ▪ Edema and ascites ▪ Hepatomegaly ▪ Jaundice ▪ Abdominal discomfort and pain
✓ **Other monitoring**	Fluid intake and output

Based on recommendations from the European Society for Blood and Marrow Transplantation (EBMT).

ALT=alanine aminotransferase ; AST=aspartate aminotransferase; HLA=human leukocyte antigen; HSCT=hematopoietic stem-cell transplantation; VOD=veno-occlusive disease.

PROMPT IDENTIFICATION IS THE FIRST STEP AGAINST VOD



DIAGNOSTIC CRITERIA FOR HEPATIC VOD[1]

Modified Seattle criteria	Baltimore 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%)	**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 and considerations of current diagnostic criteria[7]

- Late VOD onset is not considered
- VOD that presents in the absence of specified signs and symptoms, such as hyperbilirubinemia , is not considered
- Clinical judgment is an important part of diagnosis

Identify VOD and recognize the first signs of life-threatening progression

Signs of VOD progression include[12,13]:

- Early symptom onset
- Rapid disease worsening
- High magnitude of symptom severity
- Pulmonary and/or renal dysfunction

Patient Health Information: For healthcare provider use only and not to be returned to Jazz or any third parties. Documentation may be added to patient medical record.

References: 1. 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. **2.** 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. **3.** 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. **4.** Carreras E, Bertz H, Arcese W, et al; European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. *Blood.* 1998;92(10):3599-3604. **5.** Dulley FL, Kanfer EJ, Appelbaum FR, et al. Venocclusive disease of the liver after chemoradiotherapy and autologous bone marrow transplantation *Transplantation.* 1987;43(6):870-873. **6.** Dignan FL, Wynn RF, Hadzic N, et al; Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. *Br J Haematol.* 2013;163(4):444-457. **7.** 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. **8.** Corbacioglu S, Hönig M, Lahr G, et al. *Bone Marrow Transplant.* 2006;38(8):547-553. **9.** 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. **10.** 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. **11.** Carreras E. How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. *Br J Haematol.* 2015;168(4):481-491. **12.** Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. *Blood.* 1995;85(11):3005-3020. **13.** 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.

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VOD Assessment Checklist

Patient's initials: _____ Date: _____

Consider preexisting VOD risk factors (check all that apply to patient)

Patient-related risk factors	Transplant-related risk factors
Age _____ ☐ **Preexisting hepatic disturbance or dysfunction** ☐ Liver fibrosis ☐ Previous liver disease ☐ Elevated pre-HSCT AST/ALT ☐ Hepatotoxic medication ☐ Iron overload ☐ **Osteopetrosis (in children)**	☐ **Allogeneic transplant** ☐ **HLA mismatch** ☐ **Previous myeloablative HSCT** ☐ **High-intensity conditioning regimens** ☐ Oral busulfan ☐ Busulfan, in combination with cyclophosphamide ☐ **Total body irradiation (high or single dose)**

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

ALT=alanine aminotransferase; AST=aspartate aminotransferase; HLA=human leukocyte antigen; HSCT=hematopoietic stem-cell transplantation; VOD=veno-occlusive disease.

Consider daily monitoring for VOD at start of conditioning regimen and continuing for a minimum of 21 days post HSCT.

Date conditioning regimen was started: _____ Date of HSCT: _____

☐ Has VOD monitoring started? Date that monitoring started: _____

Daily monitoring (check appropriate box after monitoring for each of the following 9 signs/symptoms is completed)

1 Weight gain

Patient's baseline weight _____

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Is weight gain >2% above baseline weight at the start of the conditioning regimen?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

2 Edema and ascites	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Is edema present?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is abdominal distension/ascites present?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is patient experiencing shortness of breath?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Consider monitoring during the AM and PM

3 Abdominal discomfort/pain	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Is patient experiencing abdominal discomfort/pain?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is pain localized to right upper quadrant?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is there liver tenderness?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Consider monitoring during the AM and PM

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4 Liver function	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Are any liver function tests elevated?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Alkaline phosphatase	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Aspartate aminotransferase (AST)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Alanine aminotransferase (ALT)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Gamma-glutamyl transpeptidase (GGT)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

5 Jaundice	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Is bilirubin >2 mg/dL?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Consider monitoring during the AM and PM

6 Hepatomegaly	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Is hepatomegaly present?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Consider monitoring during the AM and PM

7 Fluid retention	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Is fluid retention present?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Consider monitoring fluid intake and output

8 Renal function	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Is serum creatinine elevated relative to the start of conditioning regimen?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Does patient require dialysis?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is glomerular filtration below normal?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Has urinary output decreased?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

9 Pulmonary function	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Does patient have blood oxygen saturation below normal?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Does patient require oxygen support?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Does patient require mechanical ventilation?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No