Identification and Management

Sinusoidal obstruction syndrome/veno-occlusive disease related to hematopoietic stem cell transplantation

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BACKGROUND: Sinusoidal obstruction syndrome (SOS), also called hepatic veno-occlusive disease (VOD), is a potentially life-threatening complication of hematopoietic stem cell transplantation (HSCT) that affects about 1 in 7 patients undergoing this procedure. SOS/VOD is caused by the conditioning regimens administered prior to HSCT; in some cases, SOS/VOD results from chemotherapy alone. SOS/VOD usually develops within three weeks following HSCT; however, it can have later onset.

OBJECTIVES: Clearly understanding how SOS/VOD develops may support prompt detection and treatment when the condition arises.

METHODS: Research on identification and management of SOS/VOD is summarized, and data from clinical trials are reviewed.

FINDINGS: This article describes the syndrome, risk factors, signs and symptoms, and appropriate supportive care and treatment. The authors also offer some practical tips for detecting SOS/VOD and providing patient care, as well as the latest information on treating and preventing this condition.

KEYWORDS sinusoidal obstruction syndrome; veno-occlusive disease; defibrotide

DIGITAL OBJECT IDENTIFIER 10.1188/18.CJON.E7-E17

Pathophysiology

HSCT conditioning may trigger a potentially rapid pathophysiologic cascade leading to SOS/VOD. Toxic metabolites of conditioning agents may activate and damage endothelial cells lining hepatic sinusoids (Carreras & Diaz-Ricart, 2011). This activation leads to loss of vascular integrity, transformation of endothelial cells from antithrombotic to prothrombotic (Hunt & Jurd, 1998), and release of inflammatory cytokines (Carreras & Diaz-Ricart, 2011).
In addition, some endothelial cells peel away from capillaries, sticking together to form emboli. Further blockage occurs when red cells, leukocytes, and cellular debris pass through the damaged endothelial lining and accumulate in the space of Disse, the perisinusoidal space between the endothelium and hepatocytes (Carreras & Díaz-Ricart, 2011; Mohty et al., 2015). The resulting obstruction of sinusoidal blood flow impedes venous outflow, extending to the portal vein system, and leads to portal hypertension (Mohty et al., 2015). These complications contribute to signs and symptoms of SOS/VOD (see Figure 1) of ascites and weight gain (Mohty et al., 2015), which may be useful indicators in adults, and expansion of abdominal girth (U.S. National Library of Medicine, n.d.), which may be a useful indicator in children, hepatomegaly, and right upper quadrant pain (Yamada, 2009). Hepatocytes (inflamed and no longer receiving adequate oxygen and nutrients from the sinusoids) become damaged and die, releasing bilirubin, which can lead to jaundice. Although jaundice is usually present in adults who develop SOS/VOD, it is often absent in pediatric patients (Mohty et al., 2015). For example, a retrospective, single-center review of 794 children who underwent HSCT found that elevated bilirubin did not occur in 5 of 17 children who developed SOS/VOD with MOD (Myers, Dandoy, El-Bietar, Davies, & Jodele, 2015).

**Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease**

Patients undergoing HSCT are susceptible to a range of serious and potentially fatal complications in addition to SOS/VOD (see Figure 2), including infections and acute graft-versus-host disease (GVHD). Overlapping symptomatology can complicate differential diagnosis of SOS/VOD. Differential diagnoses that may occur simultaneously with SOS/VOD include the following (Bearman, 1995; Kumar et al., 2003):

- Acute GVHD
- Cyclosporine-induced hepatotoxicity
- Cholangitis lenta (causes hyperbilirubinemia associated with sepsis syndrome)
- Fungal liver infection (can cause jaundice or painful hepatomegaly)

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**FIGURE 1.**

TYPICAL TIME FRAMES FOR ONSET OF SYMPTOMS RELATED TO SOS/VOD AND MOD

- Hepatomegaly/liver tenderness
- Greater than 2% weight gain
- Renal failure
- Mechanical ventilation
- Renal insufficiency
- Ascites
- Pleural effusion
- Oxygen support required
- Hyperbilirubinemia
- Edema

**Note.** Magenta boxes refer to SOS/VOD symptoms, and blue boxes refer to MOD symptoms. Time of onset of SOS/VOD and MOD is based on 190 patients from a prospective cohort evaluation of 355 consecutive patients. Rates of symptoms varied from 99.5% (bilirubin greater than 2 mg/dl) to 15.3% (mechanical ventilation). A diagnosis of SOS/VOD was made based on the occurrence of two of the following events within 20 days of transplantation: bilirubin greater than 2 mg/dl, hepatomegaly or right upper quadrant pain of hepatic origin, and sudden weight gain (greater than 2% of baseline weight). No other explanation for these signs and symptoms could be present at the time of diagnosis.

**Note.** Based on information from McDonald et al., 1993.
Constrictive pericarditis
Congestive heart failure
Pancreatic ascites
Chylous ascites
Renal failure (indicates severity with presence of SOS/VOD)
Persistent tumor infiltration into the liver
Total parenteral nutrition–related cholestasis

Because the SOS/VOD pathophysiologic cascade can progress rapidly, treatment should not be delayed to await confirmatory tests.

Factors Increasing Risk
HSCT and other risk factors for SOS/VOD, shown in Figure 3 (Carreras, 2015; Dalle & Giralt, 2016), may be additive (Carreras et al., 1998). Knowing that a patient is at heightened risk for SOS/VOD allows clinicians to be alert for SOS/VOD and minimize controllable risk, including avoiding hepatotoxic drugs, such as progestogens (Carreras, 2015), and considering RIC regimens where appropriate (Carreras et al., 1998); however, as noted previously, vigilance for SOS/VOD is still required post-RIC (Coppell et al., 2010; Tsirigotis et al., 2014).

No drugs are approved for prevention of SOS/VOD, but treatment strategies sometimes used prophylactically in high-risk patients include ursodeoxycholic acid, heparin, and defibrotide (Mohy et al., 2015). Based on available clinical evidence, preventive use of heparin is highly controversial because of bleeding risk, and studies involving ursodeoxycholic acid are inconclusive (Mohy et al., 2015). The British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation (BCSH/BSBMT) guidelines recommended prophylactic defibrotide in children (and suggest it for adults) undergoing HSCT who are at high risk for SOS/VOD (Dignan et al., 2013) based on results of a phase 3 pediatric study (Corbacoglu et al., 2012).

Assessing Severity
Assessing SOS/VOD severity to guide treatment has posed a challenge. Level of severity has historically been assessed...
Fevers commonly occur during or immediately after conditioning. The prior HSCT hepatomegaly or pain in the right upper quadrant—bilirubin greater than 1.5 mg/dl before HSCT —in children, onset of sepsis soon after HSCT—certain agents, such as cyclophosphamide and busulfan, are associated with antibiotics at the start of conditioning—bilirubin greater than 2 mg/dl (greater than 34 µmol/L) —weight gain (5% or greater from baseline weight) —ferritin levels greater than 1,000 ng/ml in children —certain genetic factors (e.g., polymorphism, such as GSTM1 or GSTT1) —underlying disease or advanced malignancy (e.g., myelodysplasia, leukemia, immunodeficiency, thalassemia) —deteriorated health status within 30 days of transplantation —impaired pulmonary function —ferretin levels greater than 1,000 ng/ml in children —prior HSCT —prior treatment of women with norethisterone or other progestins —intense conditioning using high-dose chemotherapy or total body irradiation —elevated transaminase values before HSCT; an AST to ALT ratio of 2:1 or greater suggests possible acute alcoholic hepatitis. —bilirubin greater than 1.5 mg/dl before HSCT —preexisting viral hepatitis or cytomegalovirus positivity —greater risk for young children, particularly those aged 1 year or younger —underlying disease or advanced malignancy (e.g., myelodysplasia, leukemia, immunodeficiency, thalassemia) —deteriorated health status within 30 days of transplantation —impaired pulmonary function —ferretin levels greater than 1,000 ng/ml in children —prior HSCT —prior treatment of women with norethisterone or other progestins —prior treatment with gemtuzumab ozogamicin; this agent, used to treat acute myeloid leukemia, is known to cause liver damage. —certain genetic factors (e.g., polymorphism, such as GSTM1 or GSTT1) —presence of osteoporosis in infants

**TRANSPANTATION-RELATED RISK FACTORS**
- Allogeneic transplantation poses higher risk than autologous transplantation. For allogeneic transplantations, there is higher risk associated with matched unrelated donors than with sibling donors and in unmanipulated versus T-cell–depleted HSCT.
- Intense conditioning using high-dose chemotherapy or total body irradiation generally carries a higher risk relative to reduced-intensity conditioning or fractionated radiation.
- Certain agents, such as cyclophosphamide and busulfan, are associated with an increased risk of SOS/VOD developing after HSCT, with oral busulfan presenting the highest risk.
- FEVERS commonly occur during or immediately after conditioning. The presence of fever may indicate underlying infection that could make a patient more susceptible to SOS/VOD.
- GVHD prevention using the immunosuppressant sirolimus
- Treatment with antibiotics at the start of conditioning
- In children, onset of sepsis soon after HSCT

**IDENTIFICATION AND MANAGEMENT**

**FIGURE 3.**
**PATIENT- AND TRANSPLANTATION-RELATED RISK FACTORS FOR SOS/VOD**

**PATIENT-RELATED RISK FACTORS**
Anything that has impaired patients’ liver function increases the risk for developing SOS/VOD following HSCT. Examples include the following:
- Previous liver damage (e.g., hepatitis, fibrosis, radiation to the liver or abdomen)
- Elevated transaminase values before HSCT; an AST to ALT ratio of 2:1 or greater suggests possible acute alcoholic hepatitis.
- Bilirubin greater than 1.5 mg/dl before HSCT
- Preexisting viral hepatitis or cytomegalovirus positivity
- Greater risk for young children, particularly those aged 1 year or younger
- Underlying disease or advanced malignancy (e.g., myelodysplasia, leukemia, immunodeficiency, thalassemia)
- Deteriorated health status within 30 days of transplantation
- Impaired pulmonary function
- Ferritin levels greater than 1,000 ng/ml in children
- Prior HSCT
- Prior treatment of women with norethisterone or other progestins
- Prior treatment with gemtuzumab ozogamicin; this agent, used to treat acute myeloid leukemia, is known to cause liver damage.
- Certain genetic factors (e.g., polymorphism, such as GSTM1 or GSTT1)
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**ALT**—alanine transaminase; **AST**—aspartate aminotransferase; **GVHD**—graft-versus-host disease; **HSCT**—hematopoietic stem cell transplantation; **SOS/VOD**—sinusoidal obstruction syndrome/veno-occlusive disease.

**Note.** Based on information from Barker et al., 2003; Bearman, 1995; Carreras, 2015; Carreras & Diaz-Richart, 2011; Carreras et al., 1998, 2011; Cheuk et al., 2007; Corbacioglu et al., 2006; Cutler et al., 2008; Hägglund et al., 1998; Hasegawa et al., 1998; Kashyap et al., 2002; Matute-Bello et al., 1998; Maximova et al., 2014; McDonald et al., 1993; Mora-Mora et al., 2000; Moscardo et al., 2003; Murali & Carey, 2014; Nagler et al., 2014; Rajvanashi et al., 2002; Tüngör et al., 2014; Wadleigh, Richardson, et al., 2003.

Prospectively grading severity is potentially more useful (Carreras, 2015; Chao, 2014; Mohty et al., 2016). A system proposed by the European Society for Blood and Marrow Transplantation (EBMT) (see Table 1) emphasizes clinical measurements and rate of change to assist with treatment decisions (Mohty et al., 2016). The EBMT has developed a SOS/VOD learning program for nurses, which can be accessed online (http://bit.ly/2B0Anq8).

Many SOS/VOD cases may not worsen beyond moderate severity and instead resolve within two to three weeks (Carreras, 2015). Mild cases may require only supportive care (primarily sodium/fluid restriction and diuretics) (Carreras et al., 2011). However, even in apparently mild cases, SOS/VOD can progress unpredictably and rapidly, so SOS/VOD symptoms always merit heightened vigilance, even when the cause appears to be something other than SOS/VOD. For moderate to severe SOS/VOD, comprehensive supportive care with pharmacotherapy is indicated (Carreras, 2015; Mohty et al., 2016). For SOS/VOD with MOD, start pharmacologic treatment immediately in patients without specific contraindications to treatment (Carreras, 2015).

Diagnosing
Nurses are key to early detection of SOS/VOD and, therefore, prompt treatment. In the absence of a specific diagnostic test and in light of the urgency of identifying and treating SOS/VOD, two sets of clinical criteria have traditionally been used for diagnosing SOS/VOD without the risk associated with invasive liver biopsy (Coppell et al., 2010): the modified Seattle criteria (McDonald et al., 1993) and the Baltimore criteria (Jones et al., 1987). The modified Seattle criteria involve presence of two or more of the following within the first 20 days post-HSCT (McDonald et al., 1993):
- Bilirubin greater than 2 mg/dl (greater than 34 µmol/L)
- Hepatomegaly or pain in the right upper quadrant
- Weight gain (greater than 2% of baseline weight or, in some studies, greater than 5% from baseline [Corbacioglu et al., 2012; Dignan et al., 2013; Richardson et al., 2017])

The Baltimore criteria involve presence of bilirubin greater than 2 mg/dl (greater than 34 µmol/L) plus two or more of the following within the first 21 days post-HSCT (Jones et al., 1987):
- Painful hepatomegaly
- Ascites
- Weight gain (5% or greater from baseline weight)
The EBMT issued revised diagnostic criteria for SOS/VOD in adults (Mohty et al., 2016). The proposed adult criteria adopt “classical” Baltimore criteria. However, the EBMT also recognizes late-onset SOS/VOD starting more than 21 days after HSCT (not always associated with hyperbilirubinemia), which may be diagnosed by classical criteria, histology, or hemodynamic or ultrason sound evidence of SOS/VOD plus at least two of the following: bilirubin 2 mg/dl or greater, painful hepatomegaly, and weight gain greater than 5% or ascites (Mohty et al., 2016). The Baltimore criteria require elevated bilirubin. However, SOS/VOD can occur without hyperbilirubinemia in adults with late-onset SOS/VOD or in children.

New pediatric guidelines for the diagnosis of SOS/VOD were issued by the EBMT (Corbacioglu et al., 2017) that do not require hyperbilirubinemia or include a limitation on time of onset. These guidelines require the presence of two or more of the following:
- Unexplained consumptive and transfusion-refractory thrombocytopenia
- Unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain greater than 5% above baseline value
- Hepatomegaly above baseline
- Ascites above baseline

### TABLE 1.
EBMT CRITERIA FOR SEVERITY GRADING OF SUSPECTED SOS/VOD IN ADULTS

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
<th>VERY SEVERE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since first clinical symptoms of SOS/VOD*</td>
<td>Greater than 7 days</td>
<td>5–7 days</td>
<td>4 days or greater</td>
<td>Any time</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>2 or greater mg/dl (54 μmol/L) but less than 3 mg/dl (51 μmol/L)</td>
<td>3 or greater mg/dl (51 μmol/L) but less than 5 mg/dl (85 μmol/L)</td>
<td>5 or greater mg/dl (85 μmol/L) but less than 8 mg/dl (136 μmol/L)</td>
<td>8 or greater mg/dl (136 μmol/L)</td>
</tr>
<tr>
<td>Bilirubin kinetics</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Transaminases</td>
<td>2 or less times more than normal</td>
<td>Greater than 2 but up to 5 times more than normal</td>
<td>Greater than 5 but up to 8 times more than normal</td>
<td>Greater than 8 times more than normal</td>
</tr>
<tr>
<td>Weight increase</td>
<td>Less than 5%</td>
<td>5% or greater but less than 10%</td>
<td>5% or greater but less than 10%</td>
<td>10% or greater</td>
</tr>
<tr>
<td>Renal function at HSCT</td>
<td>Less than 1.2 times baseline</td>
<td>1.2 or greater but less than 1.5 times baseline</td>
<td>1.5 or greater but less than 2 times baseline</td>
<td>2 or greater times baseline or other signs of MOD</td>
</tr>
</tbody>
</table>

*Patients with MOD must be classified as very severe.

*Time from the date when the first signs or symptoms of SOS/VOD began to appear (retrospectively determined) and the date when the symptoms fulfilled SOS/VOD diagnostic criteria

EBMT—European Society for Blood and Marrow Transplantation; HSCT—hematopoietic stem cell transplantation; MOD—multiorgan dysfunction; SOS/VOD—sinusoidal obstruction syndrome/veno-occlusive disease.

Note. Patients belong to the category that fulfills two or more criteria. If patients fulfill two or more criteria in two different categories, they must be classified in the more severe category. Weight increase from 5% or greater but less than 10% is considered, by default, a criterion for severe SOS/VOD; however, if patients do not fulfill other criteria for severe SOS/VOD, weight increase from 5% or greater but less than 10% is considered a criterion for moderate SOS/VOD.


Rising bilirubin from baseline on three consecutive days or bilirubin at least 2 mg/dl within 72 hours. Severity criteria for pediatric patients are based on measures of persistent refractory thrombocytopenia, bilirubin level and kinetics, ascites, transaminases and glutamate dehydrogenase, coagulation impairment, renal function, pulmonary function, and presence of a new cognitive impairment.

From the start of HSCT conditioning, identify patients at heightened risk for SOS/VOD by performing daily or twice-daily weight check and comparing that measurement with baseline pretransplantation weight, and monitor patients for early signs of SOS/VOD. For example, an adult with a current weight of 81.6 kg and a baseline weight of 80 kg had a 2% weight gain, and a child with a current weight of 10.5 kg and a baseline weight of 10 kg had a 5% weight gain. For this same child, a current weight of 10.2 kg versus 10 kg at baseline (only a 20-gram difference) represents a 2% gain and may be hard to distinguish from background fluctuation because of fluid retention or another cause.

### Monitoring
Nurses are crucial in recognizing, administering, and managing SOS/VOD. To increase the likelihood of promptly detecting SOS/VOD, repeatedly and thoroughly assess all patients undergoing HSCT for signs and symptoms of the condition—particularly...
patients with risk factors for SOS/VOD. Monitoring should begin with the start of conditioning and continue at least 21 days post-HSCT (Carreras, 2015). Key factors include weight gain of 2%–5% (measured daily), right upper quadrant or abdominal pain, jaundice, bleeding, and reviewing daily blood tests (see Figure 4).

Signs and symptoms indicative of possible SOS/VOD should trigger increased vigilance and supportive care to prevent progression. Supportive steps may include administering diuretics or restricting fluid intake to maintain an adequate fluid and sodium balance. Restricting fluid intake of patients with SOS/VOD can be challenging. Most will need to take drugs orally with liquid. In the authors’ experience, 30–50 ml is the smallest practical volume of liquid for adults to swallow an average-sized pill or capsule.

The progression of signs and symptoms of possible SOS/VOD justifies starting treatment with defibrotide (Carreras, 2015). When SOS/VOD develops, the condition can progress unpredictably and may rapidly become life-threatening. Rather than wait for confirmatory testing, it has been suggested that it may be better to initiate treatment if unsure whether SOS/VOD is truly present. Treatment can be halted if the patient is later found not to have SOS/VOD (Carreras, 2015).

Management of Suspected or Newly Diagnosed SOS/VOD
Management of suspected or newly diagnosed SOS/VOD requires redoubled monitoring and measures to minimize the severity of SOS/VOD and risk of progression to MOD (Carreras, 2015). The foundation of patient management at this stage is supportive care (see Figure 5), with a key goal of maintaining renal and pulmonary function, both of which can quickly become compromised.

Treating SOS/VOD
For most treatments that have been tried for SOS/VOD, compelling evidence of efficacy and tolerability is limited. For example, use of heparin is highly controversial because of bleeding risk (Mohty et al., 2015), and methylprednisolone may be considered with vigilance because of infection (Dignan et al., 2013). The drug with the most comprehensive and consistent evidence of efficacy is defibrotide, a mixture of oligodeoxyribonucleotides from porcine mucosal DNA, which is administered via IV

### FIGURE 4.
AN ACTIONABLE LIST FOR MONITORING FOR POSSIBLE SOS/VOD

**MEASURE AND RECORD FLUID INTAKES AND OUTPUTS DAILY.**
Weight gain indicative of SOS/VOD may be misattributed to IV fluids. Carefully measuring incoming and outgoing fluids can help ensure that ascites from incipient SOS/VOD is detected.

**WEIGHT PATIENTS AT LEAST ONCE A DAY.**
Weight gain caused by ascites is the first sign of SOS/VOD in most patients. Nurses should establish a baseline weight and then weigh patients daily to detect weight gain. Be particularly alert for rapid weight gain, which sometimes occurs in just a few hours, that can indicate early and potentially severe SOS/VOD. The current authors recommend twice-daily weighing for pediatric patients who have undergone HSCT, particularly if their weight is trending upward.

**CONSIDER MEASURING ABDOMINAL GIRTH DAILY.**
Repeatedly measuring the same circumference for a patient can be extremely challenging and potentially unreliable, particularly in adult patients. Such measurements may be more easily done—and provide more accurate and clinically useful results—in pediatric patients. To ensure consistent girth readings, carefully mark the area on the abdomen where measurement is taken so that variability in tape measure location is minimized.

**ASSESS FOR HEPATOMEGALY.**
This can sometimes be assessed through physical examination but often can be detected only by ultrasound.

**ASK PATIENTS DAILY IF THEY ARE EXPERIENCING PAIN.**
In particular, right upper quadrant pain or generalized abdominal pain can indicate hepatomegaly and the presence of SOS/VOD.

**EXAMINE SKIN FOR THE PRESENCE OF JAUNDICE.**
This could signal that SOS/VOD-induced liver damage is elevating blood levels of bilirubin.

**REVIEW DAILY BLOOD TEST RESULTS.**
Review absolute values and changes from baseline for critical information related to SOS/VOD. Nurses typically are the first members of the team to see results and can promptly alert colleagues to possible problems. Elevated levels of alkaline phosphatase, alanine aminotransferase, gamma-glutamyl transpeptidase, and serum bilirubin are crucial signals. In addition, elevations in serum creatinine can signal renal failure requiring hemodialysis.

**ASSESS ALL SITES FOR BLEEDING.**
Because nurses interact with patients many times per day, nurses are often aware of whether a patient has experienced even a slight bleed and where it occurred. It is also helpful to ask patients if they have noticed any bleeds.

**MONITOR FOR LATE-ONSET SOS/VOD.**
SOS/VOD has been noted to occur as many as 50 days post-HSCT, with one-third of late-onset SOS/VOD cases developing after patients have been discharged from the hospital. Continue to assess patients during postdischarge appointments, and enlist patients and caregivers in looking for signs and symptoms that may indicate SOS/VOD.

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*Note. Based on information from Carreras, 2015; Chao, 2014; Eisenberg, 2008; Jones et al., 1987; Kumar et al., 2003; McDonald et al., 1993; Sosa, 2012.*
at a recommended dose of 6.25 mg/kg every six hours (25 mg/kg per day) for 21 or more days (Jazz Pharmaceuticals, 2016a, 2016b).

In the United States, defibrotide is approved to treat adult and pediatric patients with hepatic SOS/VOD, with renal or pulmonary dysfunction post-HSCT (Jazz Pharmaceuticals, 2016a). Defibrotide is approved in the European Union for treating severe hepatic SOS/VOD post-HSCT in adults and children aged older than 1 month (Jazz Pharmaceuticals, 2016b). In addition, the EBMT and BCSH/BSBMT recommended defibrotide for treating SOS/VOD in adults and children (Dignan et al., 2013; Mohty et al., 2015). Defibrotide is not approved for prophylaxis.

Post-HSCT patients typically receive many IV infusions, so central line management is a consideration. Defibrotide may be temporarily withheld for surgical procedures or to accommodate other urgent medication without dose modification. Defibrotide administration is recommended to be completed more than two hours before surgical procedures. Dosing also may need to be scheduled around other medications and interventions, such as dialysis. It is recommended that no more than four consecutive doses be missed because of medical/surgical intervention except in the event of toxicity arising from the intervention (e.g., bleeding from central line placement).

A phase 3 trial investigating preventive use enrolled 356 pediatric patients (younger than age 18 years) receiving HSCT, all of whom had at least one risk factor for SOS/VOD (Corbacioglu et al., 2012). Patients were randomly allocated to receive either defibrotide treatment (180 patients) or standard care (176 patients). The protocol allowed all patients, regardless of assigned group, to receive defibrotide treatment if SOS/VOD developed. Twenty-two (12%) of the 180 patients in the defibrotide group developed SOS/VOD by 30 days post-HSCT, compared with 35 (20%) of the 176 patients in the control group (z-test for competing risk analysis, p = 0.0488; log-rank test, p = 0.0507). Adverse events, which were consistent with prior studies, were similar between the prophylaxis and control groups (Corbacioglu et al., 2012). Additional study is warranted to further examine the efficacy and safety profile of defibrotide for SOS/VOD prophylaxis. A phase 3, randomized study to evaluate defibrotide prophylaxis in high-risk adult and pediatric patients undergoing HSCT is underway (NCT02851407) (Richardson, Corbacioglu, et al., 2016).

**Case Study: Severe SOS/VOD in an Adult Patient**

A 37-year-old woman with chronic myeloid leukemia was treated with imatinib and then dasatinib. The leukemia transformed to acute myeloid leukemia and was treated with thioguanine, cytarabine, and daunorubicin. The conditioning regimen was IV busulfan/cyclophosphamide (busulfan is an SOS/VOD risk factor, but risk is somewhat lower with IV versus oral administration), and the patient underwent allogeneic HSCT.

**Chronology of Signs and Symptoms**

**Resolution of SOS/VOD**

**Figure 5. General Recommendations for Supportive Care of SOS/VOD and MOD**

- Position patient comfortably.
- Restrict fluid and sodium intake so as not to worsen ascites.
- Administer mild diuretics while carefully preserving renal blood flow.
- Administer blood product support (e.g., platelets, packed red blood cells, fresh frozen plasma).
- Maintain an adequate fluid and sodium balance.
- Avoid administering hepatotoxic or nephrotoxic drugs to patients.
- Administer sufficient opiate analgesia if indicated (e.g., for pain in right upper quadrant).
- Paracentesis (about 1 L per day in adults) is appropriate when ascites causes respiratory compromise. Perform with caution so as not to harm renal blood flow. In infants with massive ascites threatening respiration, early paracentesis may help to avoid complications because of assisted ventilation.
- Patients with SOS/VOD and MOD face increased risk for infection. Therefore, maintain skin integrity by discouraging patients from scratching and encouraging patting skin dry rather than rubbing.
- Administering colloids, albumin, and red blood cells to maintain a hematocrit greater than 30% can help to preserve intravascular volume.
international units per liter, gamma-glutamyltransferase 87 units per liter, aspartate aminotransferase 30 units per liter.

- Day 43: Bilirubin level was within normal range, and no clinical signs of SOS/VOD were observed.
- One year post-transplantation: The patient is in remission with normal liver function tests and has returned to work.

Preclinical and Clinical Defibrotide Studies

Preclinical studies suggest that defibrotide helps in several ways to protect hepatic endothelial cells damaged in SOS/VOD. SOS/VOD pathogenesis includes increased plasminogen activator inhibitor-1 (PAI-1) levels, which promote clot formation by preventing fibrinolysis by tissue plasminogen activator (t-PA) (Ho, Linden, Revta, & Richardson, 2007; Nurnberger, Michelmann, Burdach, & Göbel, 1998). Defibrotide selectively binds to damaged endothelial cells (Tripplett, Kuttab, Kang, & Leung, 2015) and stimulates t-PA release while decreasing PAI-1 levels, thereby encouraging fibrinolysis (Kaleelrahman et al., 2003; Wadleigh, Ho, Montaz, & Richardson, 2003). Defibrotide also exerts antithrombotic/anticoagulant effects by stimulating synthesis of thrombomodulin in endothelial cells, rendering thrombin unable to activate platelets and certain coagulant factors (Zhou, Chu, & Ruan, 1994). In addition, defibrotide protects endothelial cells from apoptosis induced by certain cytotoxic drugs and confers anti-inflammatory properties (Palomo et al., 2016; Richardson et al., 2012).

A historically controlled phase 3 treatment trial found that defibrotide significantly improved day 100 survival in patients undergoing HSCT who developed SOS/VOD with MOD (Richardson, Riches, et al., 2016). This multicenter trial involved 102 adult and pediatric patients treated with defibrotide and a comparison historic control group of 32 patients who met inclusion criteria and received standard supportive care. Survival at day 100 post-HSCT, the primary endpoint, was 38.2% among defibrotide-treated patients versus 25% in the historic control group for a statistically significant estimated difference of 13% (p = 0.009, propensity-adjusted). The median duration of treatment, 21.5 days (Richardson, Riches, et al., 2016), was similar to that observed in an earlier dose-finding study (Richardson et al., 2010), an expanded-access program (Richardson et al., 2017), and current prescribing guidelines (Jazz Pharmaceuticals, 2016a, 2016b).

The study's key secondary measure was day 100 complete response (CR) rates, defined by bilirubin less than 2 mg/dl plus resolution of MOD. The CR rates were 25.5% (26 patients) for defibrotide-treated patients and 12.5% (4 patients) for controls, yielding a statistically significant difference of 13% (p = 0.016, propensity-adjusted).

Defibrotide also appears to be promising in treating SOS/VOD without MOD (Richardson et al., 2017), but it is not approved for this use. A study designed to provide expanded access to defibrotide, which had no comparison arm, gathered data on patients who had SOS/VOD with and without MOD. Interim results for 222 patients without MOD found a 58% survival rate at day 100, and 351 patients with MOD had a 45% survival rate (Richardson et al., 2017).

A subsequent exploratory analysis of post-HSCT patients in the expanded-access study assessed the relationship between day 100 survival and number of days from SOS/VOD diagnosis to initiation of defibrotide. Survival rates for pediatric and adult patients showed a statistically significant trend over time (p < 0.001 and p = 0.028, respectively, using the Cochran-Armitage test) for better day 100 survival with earlier treatment initiation (Grupp et al., 2016).

Defibrotide Safety Profile

The phase 3 treatment trial found generally comparable rates of adverse events between treatment and control populations, including common hemorrhagic (64% and 75%, respectively), hypotensive (39% and 50%, respectively), and fatal (64% and 69%, respectively) adverse events (Richardson, Riches, et al., 2016). The adverse events most likely associated with defibrotide include abdominal distress, epigastric pain, injection site reactions, nausea, vomiting, and hemorrhage (Richardson et al., 2013; Richardson, Riches, et al., 2016), so treated patients should be monitored for signs of bleeding, with blood product support administered as clinically indicated.

No safety issues have been identified in patients with serious hepatic impairment, and defibrotide is not metabolized by cytochrome P450 (Jazz Pharmaceuticals, 2016a, 2016b). Therefore, no dose adjustment is recommended for patients with renal or hepatic impairment (Jazz Pharmaceuticals, 2016b). Because defibrotide’s fibrin-dissolving effect may enhance the activity of antithrombotic and fibrinolytic drugs (Keating, 2014), these
Recognize factors that increase patient risk for sinusoidal obstruction syndrome/hepatic veno-occlusive disease (SOS/VOD), an unpredictable and potentially life-threatening condition that may occur after hematopoietic stem cell transplantation (HSCT).

Increase vigilance when monitoring for signs and symptoms of SOS/VOD, which may mimic other post-HSCT complications.

Initiate supportive measures for symptoms of SOS/VOD as soon as possible; prompt treatment with defibrotide in patients with SOS/VOD is associated with increased survival compared with later treatment.

Communicating With Patients and Family Members

Nurses spend substantial time talking with patients and families, who should be given honest, compassionate, up-to-date information about a patient’s condition. Family members may have searched the Internet for “SOS” or “VOD,” and their findings may distress them. Be prepared to respond and, in particular, note that the historic, retrospective definition of “severe” SOS/VOD included all patients who died, so it is not equivalent to the EBMT’s current, prospective assessment of severity (Mohty et al., 2016). In addition, SOS/VOD can cause significant changes in body image (from ascites, edema, and jaundice), which may have profound physiologic and psychological implications for patients and family (Eisenberg, 2008).

The SPIKES strategy for delivering difficult news (Baile et al., 2000) may be helpful in providing information to patients and families.

- **S**—Setup. To minimize distractions, select a quiet, private location.
- **P**—Perception. Determine what the patient/caregivers already know and whether they have misconceptions. Remember that prognosis for SOS/VOD has changed over time and that every case is unique (e.g., not everything on the Internet is current or applicable).
- **I**—Invitation. Find out how much the patient/caregivers want to know (e.g., as much as possible or just the next treatment step).
- **K**—Knowledge. Tailor information to the specific needs of each patient and family. Explain the situation in terms that will be clear to them, and allow a moment for them to absorb information. Before discharging patients, caution them that SOS/VOD can have a long-lasting legacy, and it may take several months before liver function has normalized.
- **E**—Empathize. Provide emotional support while being realistic about the medical situation and answering patient and family questions. Reassure them that support, treatments, and resources are available to control pain and other symptoms.
- **S**—Summarize. Make sure the information was understood.

**Conclusion**

Nurses have a frontline role in recognizing the signs and symptoms of SOS/VOD, providing supportive care, and communicating compassionately with patients and families. SOS/VOD is potentially life-threatening and can progress rapidly and unpredictably, so early detection of signs and symptoms, including weight gain, ascites, hepatomegaly, right upper quadrant pain, and hyperbilirubinemia, is critical. Diagnosing SOS/VOD can be challenging because other post-HSCT complications can mimic its signs and symptoms, so vigilance is crucial. Defibrotide has been approved for treating hepatic SOS/VOD with renal or pulmonary dysfunction post-HSCT in the United States (Jazz Pharmaceuticals, 2016a) and severe hepatic SOS/VOD post-HSCT in the European Union (Jazz Pharmaceuticals, 2016b).

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