CPE

# Pharmacy Practice in the Management of VOD/SOS: Developing Optimal Care Models and Modern Therapeutic Arsenals

PeerView inReview


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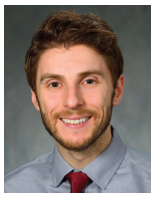

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**What's Inside**




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## Activity Information

**Activity Description and Educational Objectives**
In this activity, an expert in VOD/SOS discusses the pharmacist's perspective on optimal care models and the use of modern therapeutic arsenals for the recognition and management of VOD/SOS in cancer patients undergoing stem cell transplantation.

Upon completion of this activity, participants will be able to:
- Cite the medical and financial burden of untreated or inadequately treated VOD/SOS, including VOD with MOD/MOF
- Summarize pre-transplant therapies that may elevate the risk for VOD/SOS in cancer patients
- Select therapeutic options for VOD/SOS prevention and treatment based on the latest clinical evidence
- Discuss dosing and safety considerations with conventional and novel options for VOD/SOS prevention or treatment

**Target Audience**
This activity has been designed to meet the educational needs of pharmacists and other clinicians involved in the care of transplant-eligible cancer patients at risk for VOD/SOS.

**Requirements for Successful Completion**
In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CPE credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CPE credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

Media: Enduring Material
Release and Expiration Dates: November 10, 2017 - November 09, 2018
Time to Complete: 30 minutes

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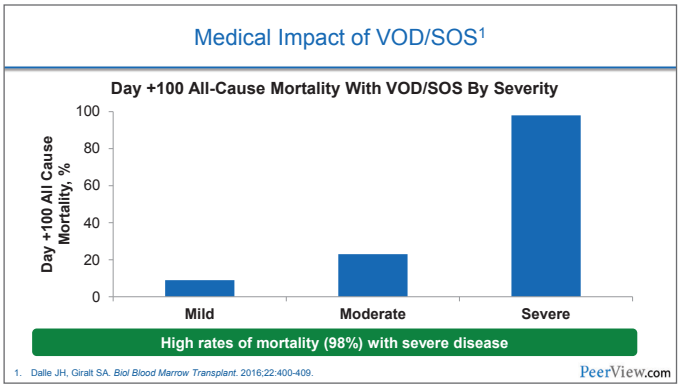
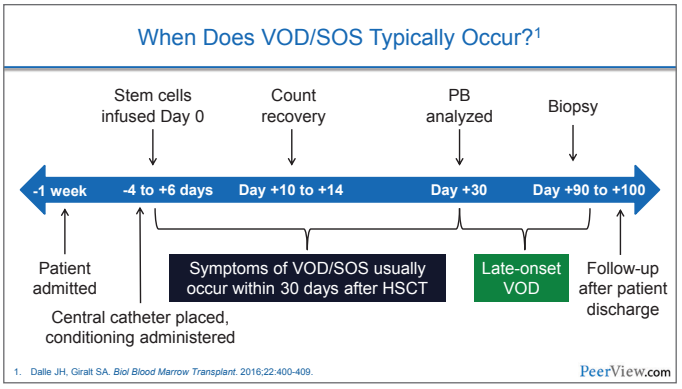
## The Pharmacy Perspective on VOD/SOS Risk Factors and Diagnosis

**Dr. Ganetsky:** Hello, this is Dr. Alex Ganetsky from the Hospital of the University of Pennsylvania. Welcome to this educational activity on the management of VOD/SOS, which will feature a pharmacy perspective on many aspects of care.



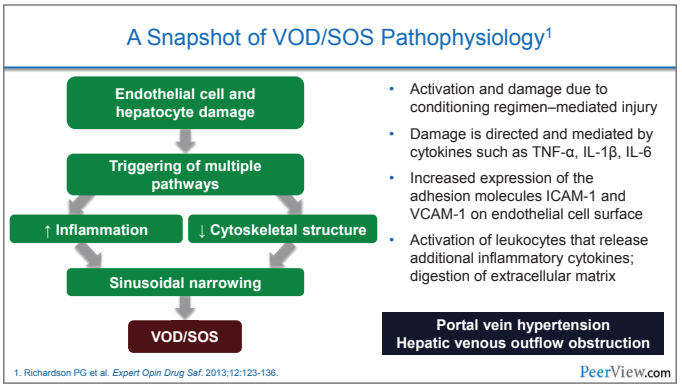

VOD is one of the potentially life-threatening complications that stem cell transplant recipients are predisposed to. The trajectory of VOD is quite different depending on the severity of the disease, wherein the majority of cases are mild to moderate in nature, and most patients do fine with standard supportive care, as long as diagnosis and treatment is initiated early.

However, patients with severe VOD have a very different trajectory, as the day +100 all-cause mortality for these patients is upwards of 95%, 96%. And this is the patient population that clinically we are really concerned about.




When does VOD/SOS typically occur? So, the majority of cases—about 80% to 85% of cases—occur within the first 3 to 4 weeks after stem cell transplantation. It's one of the early onset complications within the ever-expanding chronology of stem cell transplant complications that may arise.

Importantly, within the last 5 to 7 years, there has been an increased incidence of late-onset VOD cases occurring after the traditional 3- to 4-week window, and now, about 15% to 20% of cases occur after this timeframe. And thus, it's important to remain cognizant of the possibility of VOD developing not within the traditional timeframe.




VOD/SOS arises from endothelial cell damage and hepatocellular injury due to toxic metabolites that are generated from the high-dose chemotherapy and/or radiation therapy that's part of the conditioning regimen. This then leads to increased expression of various cell adhesion molecules on the endothelial cell surface, causing the activation of leukocytes that release additional inflammatory cytokines, ultimately culminating with the narrowing of the sinusoids and veno-occlusive disease.

### Summary of Patient-Related Risk Factors for VOD/SOS[1,2]

| Factor | Relative Risk |
|---|---|
| Age | Adolescent/adult < children or elderly |
| Health status | Normal < comorbidities and poor performance status |
| Diagnosis | Nonmalignancy < malignancy < specific malignancies/ high-risk conditions (eg, MF)[a] |
| Disease status | Remission < advanced |
| Liver status | Normal < hepatitis, iron overload, fibrosis, cirrhosis |
| Prior liver disease | No < yes |
| Previous drugs | Gemtuzumab/ozogamicin, inotuzumab/ozogamicin |

[a] Hemophagocytic lymphohistiocytosis, adrenoleukodystrophy, osteopetrosis, and thalassemia (benign, but higher risk).
1. Carreras E. *Br J Haematol.* 2015;168:481-491. 2. Kebriaei P et al. *Clin Lymphoma Myeloma Leuk.* 2013;13:296-301.
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### Summary of Transplant-Related Risk Factors for VOD/SOS[1,2]

| Factor | Relative Risk |
|---|---|
| Type of HSCT | Syngeneic/autologous < allogeneic |
| Grade of compatibility | Match < minor mismatch < major mismatch |
| Origin of stem cells | PB < BM/TCD < non-TCD |
| Conditioning regimen | |
| Total dose | RIC < MAC |
| Busulfan | IV < oral dose targeted < oral nonadjusted |
| Administration order | Cy + Bu < Bu + Cy |
| GVHD prophylaxis | Without CNI < with CNI < CNI + sirolimus |
| Other hepatotoxic drugs | No < yes |
| HSCT number | First < second |

1. Carreras E. *Br J Haematol.* 2015;168:481-491. 2. Kebriaei P et al. *Clin Lymphoma Myeloma Leuk.* 2013;13:296-301.
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There have been a number of different predisposing factors associated with VOD/SOS over the years. Some have been longstanding. Others we have recently learned about. And I like to group risk factors for VOD/SOS within two buckets: the patient-related risk factors and the transplant-related risk factors.

So, with respect to the most common patient-related risk factors, older-aged patients with poor performance status or multiple comorbidities going into treatment have a higher risk. Patients with active disease at the time of transplant have a higher risk than those in remission.

Now, this is an important risk, given that globally the predisposition to VOD is driven by the degree of alloreactivity. And thus, patients who have active disease at the time of transplant have a higher degree of alloreactivity, and thus a higher risk of veno-occlusive disease.

In addition, patients with preexisting liver injury—either patients with hepatitis or a history of iron overload, fibrosis, cirrhosis—all have a high risk of VOD/SOS. Recently, a number of drugs have received FDA approval for the treatment of either AML (specifically gemtuzumab/ozogamicin) or for ALL (inotuzumab/ozogamicin), and both of these agents predispose patients to a higher risk of VOD/SOS after they've been treated and are then going to transplant.

Thus, it's critically important to remain cognizant of prior drug therapy that patients may have received before their stem cell transplant in order to better characterize their risk and then possibly identify optimal prophylaxis strategies.

What are the most common transplant-related risk factors?

Going along the theme of the degree of alloreactivity, promoting patients' predisposition to VOD/SOS, the type of transplant is a significant risk factor. So, allogeneic stem cell transplantation is associated with a significantly greater risk than either a syngeneic or an autologous transplant.

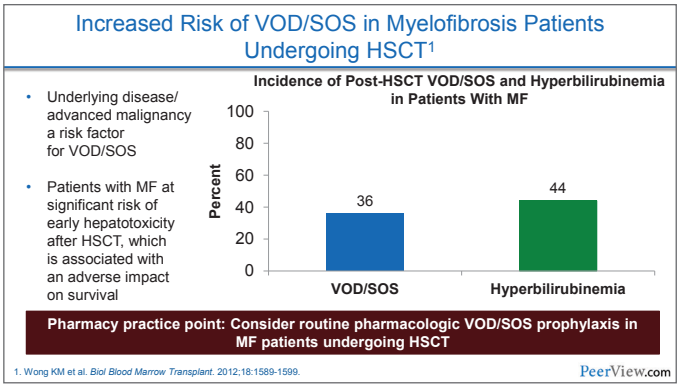
Patients who have a mismatched donor transplant have a higher risk. Patients undergoing a myeloablative conditioning regimen have a higher risk than those undergoing a reduced-intensity conditioning regimen.

Certain parts of the conditioning regimen themselves can predispose patients to a higher risk. We recently learned from the Fred Hutchinson Cancer Center that if you reverse one of the most common conditioning regimens, which is busulfan coadministered with cyclophosphamide, the Bu/Cy regimen, the risk of VOD/SOS is less.

In addition, the GVHD prophylaxis regimen that is selected can influence the risk, as the addition of sirolimus to a calcineurin-inhibitor–based backbone is associated with a higher risk compared with a nonsirolimus-based therapy.

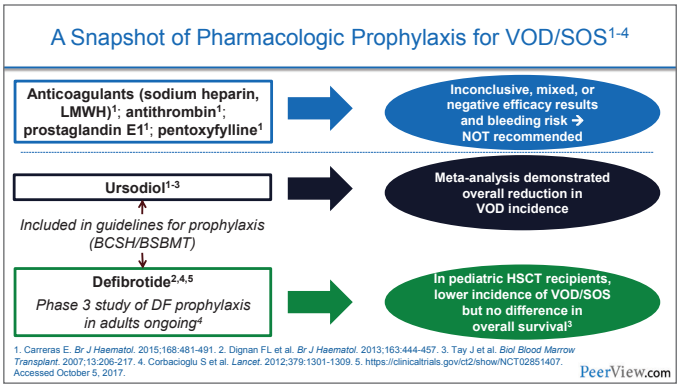
The coadministration of hepatotoxic medications can also augment the risk, given the effect on liver function. Patients who are undergoing a second transplant have a higher risk than those undergoing a first transplant.

So, this is a fairly comprehensive list of the different patient- and transplant-related risk factors that could predispose one's risk to VOD/SOS.




One of the emerging risk factors for VOD/SOS is an underlying diagnosis of myelofibrosis. Just a few years ago, we learned that patients who have an underlying diagnosis of myelofibrosis have a significantly higher risk of VOD/SOS. About 36% of patients develop the syndrome, and about 44% of patients do develop a degree of liver injury, given the inherent risks of myelofibrosis on liver function.

And so, this has become one of the diseases in which, at least in our practice, we have implemented routine pharmacological VOD/SOS prophylaxis, given the significantly higher produced position that patients with MF have with respect to developing VOD/SOS.




The optimal pharmacologic prophylaxis strategy for VOD/SOS remains unknown, despite a number of trials that have been performed over the last 15 to 20+ years.

That being said, there are three agents that have garnered the most interest. One is using anticoagulation. Given the prothrombotic nature of this complication, many different anticoagulants have been studied, heparin, low molecular weight heparin, others as well. The data for the most part have been inconclusive.

A recent meta-analysis was completed which showed that anticoagulation did not reduce the incidence of VOD/SOS, but did increase the risk of bleeding. And thus, at this time, anticoagulation as a pharmacologic prophylaxis strategy against VOD/SOS is not recommended.

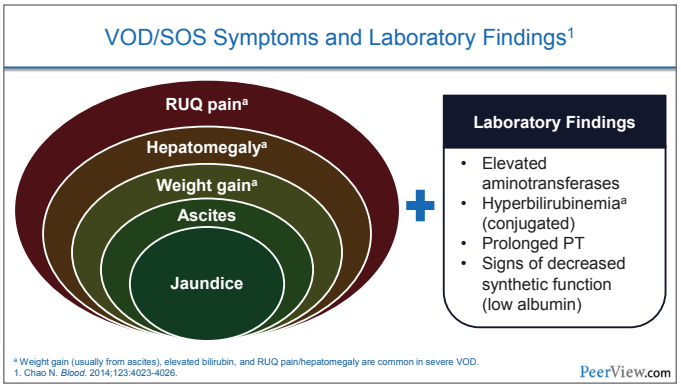
Ursodiol is a hydrophilic bile acid, which has been used for years for this syndrome. There have been a number of trials that have evaluated the efficacy of ursodiol prophylaxis for VOD/SOS. Some data were positive. Other data were not. And thus, a meta-analysis was done to evaluate all randomized trials looking at the potential role of ursodiol for prevention of this syndrome.

And what that meta-analysis showed is that ursodiol did reduce the risk of VOD incidence by about 60%—a relative risk reduction by about 60%—and thus, it is one of the recommended agents for prophylaxis against VOD/SOS.

And then, finally, defibrotide, which is an interesting compound that was approved for the treatment of VOD/SOS back in March of 2016. It is not approved for prophylaxis against VOD/SOS. There is an ongoing phase 3 trial in adults, and so results remain to be seen on whether or not this agent is effective for preventing VOD/SOS in adults.

In 2012, there was a trial that was done in Europe, specifically evaluating defibrotide prophylaxis in pediatric stem cell transplant recipients. Compared with placebo, defibrotide did reduce the incidence of VOD/SOS, but there was no difference in overall survival.

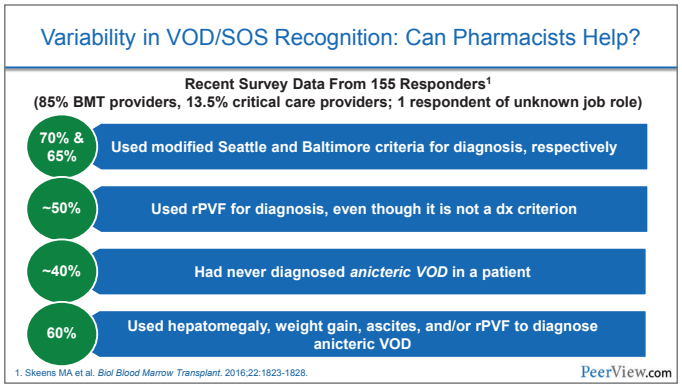
Thus, in the United States this is not an approved agent for prophylaxis against VOD/SOS, although in Europe, as well as in Britain, it is recommended for prophylaxis against the syndrome.




The most common symptoms associated with VOD/SOS include right upper quadrant pain, hepatomegaly, and weight gain. Some patients complain of ascites, and patients with severe VOD/SOS develop jaundice.

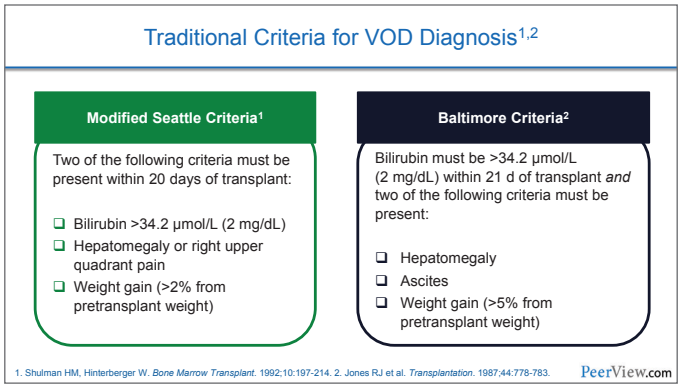
The most common laboratory findings include elevated AST/ALT. Most commonly, patients present with hyperbilirubinemia, and those with severe VOD/SOS present with rapidly escalating hyperbilirubinemia. Patients can also have a prolonged PT, as well as decreased albumin.

Interestingly, the other finding that could be suggestive of VOD is that many patients with severe VOD or rapidly progressive VOD become platelet-refractory despite repeated transfusions. So, this is another aspect that I think is important to monitor when working up for a potential diagnosis of the syndrome.




Recently, data were published to show just how variable recognition is with respect to diagnosing VOD/SOS. And in a recent survey of over 150 BMT providers there was significant heterogeneity with exactly how diagnosis for the syndrome was pursued. It appeared that about two-thirds of responders did use one of the appropriate, retrospectively devised diagnostic criteria—either the modified Seattle or Baltimore criteria. Others used rPVF for diagnosis. Some responders had stated that they had never diagnosed anicteric VOD in a patient before. And a little over half used a compilation of symptoms, such as hepatomegaly, weight gain, ascites, and/or rPVF to diagnose anicteric VOD.

So, as you can see, there is significant heterogeneity and variability with respect to the recognition of the syndrome.

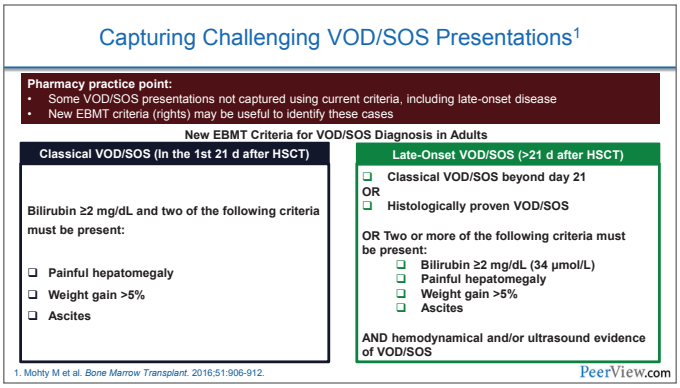



The best way to diagnose VOD is with pathologic confirmation with a biopsy, but given that many of these patients are critically ill, they have low platelets and low white cells, so it is not always feasible to pursue an invasive procedure, we have to rely on alternative measures for diagnosis.

Now, traditionally, there are two retrospectively devised criteria for VOD diagnosis that may be used. One is more permissive for diagnosis. The other is more restrictive. So, the original criteria are the Seattle criteria, which were then modified to become a little bit more stringent. And the modified Seattle criteria now require two of the following criteria to be present within the first 20 days of transplant in order to make a positive VOD diagnosis: patients have to have an elevated bilirubin, presence of hepatomegaly or right upper quadrant pain, or a greater-than-2% weight gain from their pretransplant weight.

The Baltimore criteria are more restrictive for diagnosis. In order for patients to have a positive diagnosis for VOD, patients must have an elevated bilirubin within the first 3 weeks of transplant, and two of the following criteria must be present: hepatomegaly, ascites, or a greater-than-5% weight gain from their pretransplant weight.

So, you can see that the Baltimore criteria are a bit more stringent, and thus, when epidemiologic studies have been done to evaluate the incidence of VOD/SOS, the data are really quite variable. One of the reasons for the variability is that there are different diagnostic criteria used. And when centers have used the modified Seattle criteria, the incidence is much higher than centers that use the Baltimore criteria.



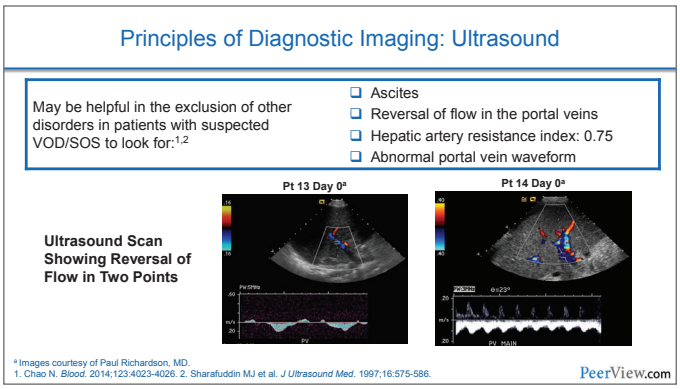

I mentioned earlier in the presentation that about 15% to 20% of cases do not occur within the traditional 3- to 4-week timeframe. And given that, these cases were being missed.

And so, just recently the European Blood and Marrow Transplant Group (EBMT) published revised diagnostic criteria. In these criteria, they advocate to use the Baltimore criteria in order to detect VOD during the classic timeframe—within the first 21 days.

But they have also set forth diagnostic criteria for late-onset VOD, which is really the first time that we have had criteria to help detect VOD cases that occur outside of the traditional timeframe.

And so, what the EBMT group recommends is that if patients meet the Baltimore criteria at any time post-transplant, either after or before day 21, it is permissible to make a VOD diagnosis.

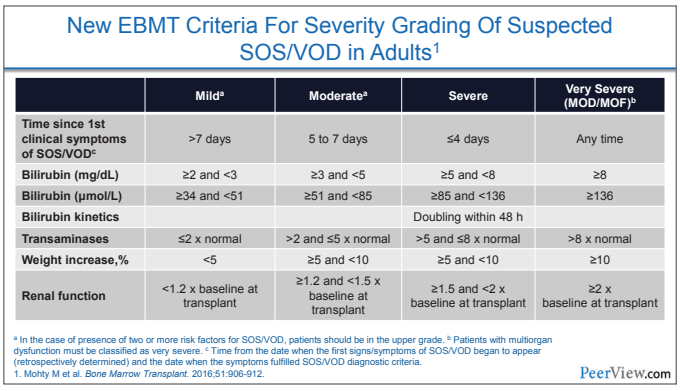
The other set of criteria that the EBMT group recommends in order to detect late-onset VOD, is that patients must have two or more of the following criteria: after the first 21 days post-transplant, either an elevated bilirubin, painful hepatomegaly, weight gain greater than 5% from their pretransplant weight, or ascites and any evidence of hemodynamic or ultrasound confirmation of VOD/SOS.




What ultrasound evidence of VOD/SOS implies is the detection of reversal of portal venous flow. If you think about what may cause patients that are within the first few weeks after stem cell transplant to have an elevated bilirubin, to have right upper quadrant pain, to develop ascites, there are a number of causes that come up on the differential.

Now, these can include abscesses, infections, and drug toxicity. VOD is just one of them. And thus, it is important to implement measures to help exclude other disorders that can mimic some of the symptomatology associated with VOD. And one of the best ways to do that is with an ultrasound.

The hallmark finding on a liver ultrasound for someone with VOD is the reversal of flow in the portal veins, in addition to an elevated hepatic artery resistance index. And some patients may have the detection of an abnormal portal vein waveform.

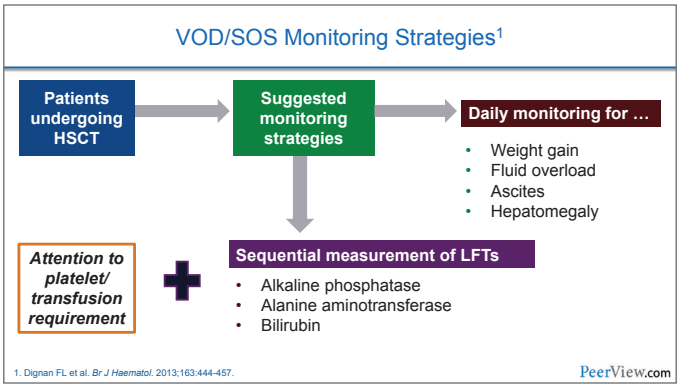



| | Mild[a] | Moderate[a] | Severe | Very Severe (MOD/MOF)[b] |
|---|---|---|---|---|
| Time since 1st clinical symptoms of SOS/VOD[c] | >7 days | 5 to 7 days | ≤4 days | Any time |
| Bilirubin (mg/dL) | ≥2 and <3 | ≥3 and <5 | ≥5 and <8 | ≥8 |
| Bilirubin (µmol/L) | ≥34 and <51 | ≥51 and <85 | ≥85 and <136 | ≥136 |
| Bilirubin kinetics | | | Doubling within 48 h | |
| Transaminases | ≤2 x normal | >2 and ≤5 x normal | >5 and ≤8 x normal | >8 x normal |
| Weight increase,% | <5 | ≥5 and <10 | ≥5 and <10 | ≥10 |
| Renal function | <1.2 x baseline at transplant | ≥1.2 and <1.5 x baseline at transplant | ≥1.5 and <2 x baseline at transplant | ≥2 x baseline at transplant |

The EBMT Group, in addition to the revised diagnostic criteria, has also come up with a revised severity grading of suspected VOD/SOS to help predict the trajectory of this disease. As you recall from one of the earlier slides in this talk, the prognosis is quite different, depending on whether patients have mild-to-moderate disease or severe disease. And this will become even more important when we discuss the treatment options for VOD.

And so, basically patients with severe VOD-have bilirubin that's greater than 5; bilirubin that's doubling within 48 hours; AST/ALT that is greater than 5 times the upper limit of normal; weight gain that's greater than or equal to 5% to 10%; and abnormal renal function.

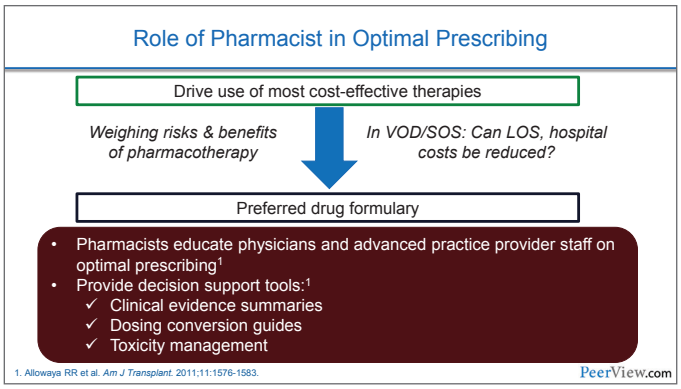
All of these criteria help to group patients into a severity stratification, which will ultimately help guide treatment.




In order to appropriately monitor VOD/SOS, there are some strategies that are recommended. It's recommended for all patients undergoing stem cell transplant to monitor daily for weight gain, for fluid overload, and also for the development of ascites and/or hepatomegaly. It is recommended to monitor liver function tests at least twice a week, if not more, depending on preexisting liver injury presence or absence.

And then, one of the other interesting markers of the development of VOD is, again, patients can become refractory to platelet transfusions. You can transfuse these patients over and over, but their platelets don't bump. And if this is occurring in conjunction with some of the traditional symptoms associated with VOD/SOS, such as weight gain, ascites, hyperbilirubinemia, this can certainly help to further confirm a diagnosis of the syndrome.

# Treating VOD/SOS and the Role of the Pharmacist

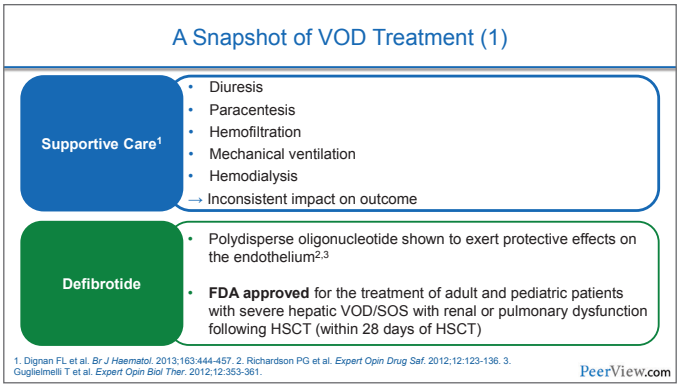



**Dr. Ganetsky:** What are the treatment options we have for patients with VOD/SOS, and what's the role of the pharmacist in this field? Well, certainly PharmDs have and continue to play a critically important role in prescribing different medications, especially life-saving medications pertaining to the field of stem cell transplantation. PharmDs certainly play a critical role in promoting the use of most cost-effective therapies.

PharmDs are responsible for providing comprehensive education for novel therapies, for providing updated guidelines to physicians, to advanced practice providers, certain nursing staff, and to other ancillary staff as well. And taken together, PharmDs play a critical role in selecting drug formulary for different medical centers.

And so, for example, with respect to VOD/SOS, there is now a drug that is FDA approved for the treatment of severe VOD/SOS, which is defibrotide. PharmDs can play a critical role in ensuring that the drug has been reviewed by the P&T committee for formulary addition at an appropriate timeframe, and that there is drug maintained in stock on hand in case there is an emergent case of VOD/SOS. And I'll talk a little bit later about the importance of early initiation of therapy.

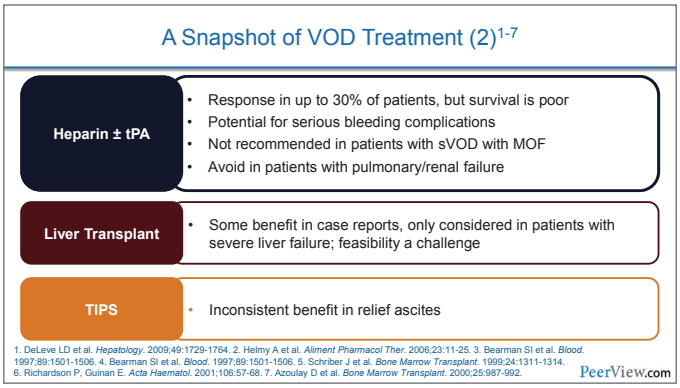
PharmDs also play a critical role in developing clinical evidence summaries, dosing conversion guidelines, as well as toxicity management. So, really comprehensive responsibilities that PharmDs play in all different therapeutic areas specifically with [respect to] therapies [in those patients] undergoing stem cell transplant who develop VOD/SOS.




So, for patients with VOD/SOS, the goal of therapy has been supportive care, which aims to minimize extracellular fluid overload without worsening renal function. Maintenance of baseline weight is also another important goal of therapy, and there are different supportive care measures that can be implemented to achieve these goals, which can include diuresis, paracentesis, and at times mechanical ventilation or dialysis, depending on whether patients have pulmonary or renal compromise, respectively.

In March of 2016, defibrotide, which is a polydispersed oligonucleotide that was shown to have protective effects on the endothelium, as well as the potential ability to restore the thrombotic-fibrinolytic balance that's lost in VOD/SOS, was approved for the treatment of adult and pediatric patients with severe VOD/SOS who have either renal or pulmonary involvement following a stem cell transplant within 28 days post transplant.

This is considered a significant advance for a rather orphan disease which has never had an FDA-approved therapy in the past.

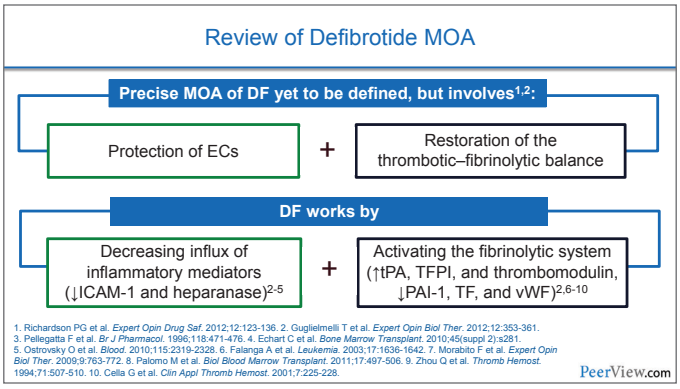



There have been other treatment options that have been evaluated over the years. Heparin, either alone or in conjunction with tPA has been evaluated, but responses have been mixed and there are some significant downsides to this therapy due to the serious bleeding complications that may arise, and thus, this therapy is not routinely used.

There are some anecdotal case reports of a liver transplant having benefit in patients with fulminant liver failure due to VOD/SOS, but it's logistically very, very challenging to push forward with a liver transplant after someone has had a stem cell transplant. Especially, many of these patients will be in the midst of the early portion of their stem cell transplant.

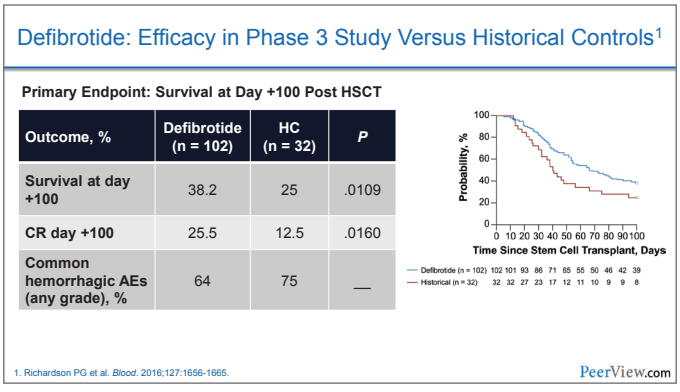
A TIPS procedure has been used as well, but has really shown some inconsistent benefit.

So, for the most part, the treatment pathway for VOD/SOS involves supportive care plus/minus defibrotide, depending on whether the VOD presentation is severe or not.




How defibrotide works has yet to be defined. It is thought to have activity in promoting the integrity of the endothelium, as well as restoring the thrombotic fibrinolytic balance that's lost in VOD/SOS by various mechanisms.

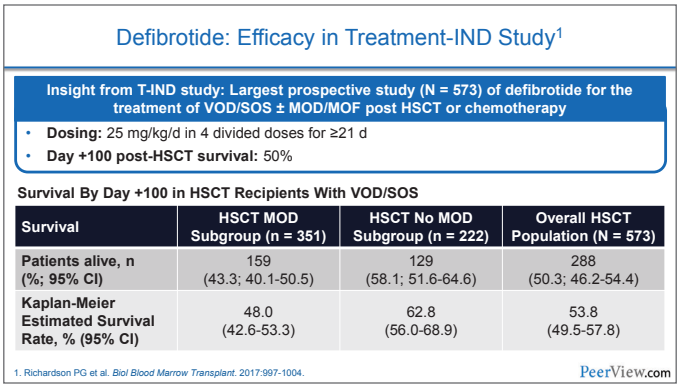
One mechanism that it is believed to be involved is thought to help decrease the influx of various inflammatory mediators that can help promote the pathogenesis of VOD. Defibrotide may also help activate the fibrinolytic system, which can ultimately restore the prothrombotic, hypofibrinolytic shift that is ongoing. But ultimately, the comprehensive mechanism has not been delineated, and a lot of work is ongoing to help better decipher the full mechanism [of action] of this drug.




Defibrotide has been studied in a number of trials for VOD/SOS. The pivotal registrational trial was a phase 3 study. It was a single-arm trial in which patients were treated with defibrotide, and then, their outcomes were compared with a historical control group. The primary endpoint of this trial was survival at day +100 post transplant.

As you can see on this slide, the survival rate was significantly improved in patients who received defibrotide at about 38% versus 25% in the historical control arm. And then, as expected, given the survival benefit, patients had a higher CR rate with defibrotide.

The most common toxicity that is a concern with defibrotide is bleeding. There did not appear to be an increased risk of bleeding with defibrotide compared with a historical control arm, which was treated with supportive care and some of the other measures that I had mentioned earlier.




In an updated analysis that was recently published in BBMT led by Paul Richardson, in a treatment IND study, which is really the largest prospective study of defibrotide for the treatment of VOD/SOS in patients who have multiorgan dysfunction, there were 573 patients who were treated with defibrotide at a dose of 25 mg/kg per day, but importantly divided in four doses and treated for at least 3 weeks. This is the FDA-approved dosing.

The survival rate was 50% at day +100 post transplant, which is really quite impressive, given how poor survival is for patients with VOD/SOS, especially those who have multiorgan failure.

## Defibrotide Safety (T-IND)[1]

**Defibrotide was generally well tolerated with manageable toxicity; no new safety signals observed**

| TEAE | MOD Subgroup (n = 351), n (%) | No MOD Subgroup (n = 222), n (%) | HSCT Population Overall (N = 573), n (%) |
|---|---|---|---|
| Hypotension | 59 (16.8) | 20 (9.0) | 79 (13.8) |
| MOD | 54 (15.4) | 19 (8.6) | 73 (12.7) |
| Progression of VOD/SOS[a] | 48 (13.7) | 9 (4.1) | 57 (9.9) |
| Pulmonary hemorrhage | 30 (8.5) | 12 (5.4) | 42 (7.3) |
| Renal failure | 28 (8.0) | 15 (6.8) | 43 (7.5) |
| Respiratory failure | 27 (7.7) | 25 (11.3) | 52 (9.1) |
| Diarrhea | 26 (7.4) | 17 (7.7) | 43 (7.5) |
| Vomiting | 24 (6.8) | 10 (4.5) | 34 (5.9) |
| Pyrexia | 23 (6.6) | 17 (7.7) | 40 (7.0) |
| GI hemorrhage | 22 (6.3) | 13 (5.9) | 35 (6.1) |
| Hypoxia | 20 (5.7) | 11 (5.0) | 31 (5.4) |
| Nausea | 20 (5.7) | 11 (5.0) | 31 (5.4) |
| Epistaxis | 15 (4.3) | 12 (5.4) | 27 (4.7) |

[a] All patients who developed VOD/SOS at any time following HSCT were included in this analysis.
1. Richardson PG et al. *Biol Blood Marrow Transplant.* 2017;23:997-1004.

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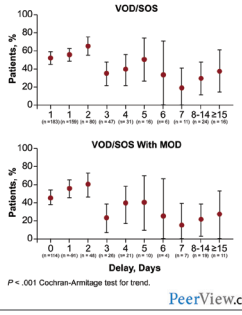
The toxicity profile of defibrotide in this treatment IND analysis was really consistent with what the pivotal phase 3 trial showed, which ultimately led to approval of this drug. The most concerning toxicity is bleeding, but the incidences appear fairly low. But nevertheless, it's important to remain cognizant when treating patients with this agent.

## Earlier Initiation of Defibrotide Linked With Better Outcomes Post HSCT[1]

- N = 573; DF started on day of dx in ~30%, within 7 days in >90%
- Significantly superior day +100 survival when treatment was initiated closer to VOD/SOS dx ($P < .001$)

**Pharmacy practice point:**
Consider protocols for immediate/early initiation of DF in patients diagnosed with severe VOD/SOS post HSCT




$P < .001$ Cochran-Armitage test for trend.

1. Richardson PG et al. *Br J Haematol.* 2017;178:112-118.

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Some of the most important data I think that we can discuss are data that were just published in the *British Journal of Haematology*. It was initially presented at the American Society of Hematology 2016, and then recently published in the *British Journal of Haematology*, and shows how critical early initiation of defibrotide is with respect to optimizing outcomes in patients post treatment who develop VOD/SOS. And what we have learned is that early initiation of therapy, especially within the first 48 hours of diagnosis of severe VOD, can significantly improve overall survival compared with delayed initiation of therapy.

And again, I think it's really, really important to work up a patient, if one is concerned for a VOD diagnosis, and then once the diagnosis is made, stratify according to severity. And if patients have severe VOD, then prompt initiation of defibrotide can be a life-saving measure, given the data that were found by this group.

## Defibrotide: Practical Considerations for Pharmacists (1)

**Dosing:** 6.25 mg/kg every 6 hours given as a 2-hour IV infusion

**Pearls for Pharmacy Practice**

- Short half-life (0.71 hours)
- Not removed by dialysis
- Contraindicated with systemic anticoagulant, fibrinolytic therapy

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But just some practical considerations for pharmacists who may be dealing with defibrotide—so, this is a drug that has a very short half-life, and thus, it is administered every 6 hours. It's given four times a day as a 2-hour infusion. Importantly, it's not removed by dialysis. This is an important pharmacokinetic pearl to note, given that many patients with severe VOD present with underlying renal dysfunction, which may warrant dialysis to aid in the reversal of the evolution of this disease, and thus, it is important to know that it is permissible to continue defibrotide despite a dialysis requirement, given that this drug is not removed by dialysis.

Because of the bleeding risk associated with this drug, it is contraindicated in patients who require systemic anticoagulation or concurrent fibrinolytic therapy.

## Defibrotide: Practical Considerations for Pharmacists (2)

**Treatment Modifications**

- **Severe hypersensitivity:** permanently discontinue
- **Bleeding (first episode):** hold, treat bleed, consider resuming at same dose once bleeding has stopped and patient is hemodynamically stable
- **Recurrent bleeding:** permanently discontinue
- **Invasive procedure:** discontinue ≥2 hours before procedure, resume post procedure, if no bleeding

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Furthermore, there have been reports of hypersensitivity with defibrotide, and thus, if someone develops severe hypersensitivity, the recommendation is to permanently discontinue the drug.

How do you manage a bleed for someone who is on defibrotide? So, if this is the first episode of a bleed that the provider deems related to defibrotide, the recommendation is to hold the drug, treat the bleed, and then once the bleed has stopped and the patient is hemodynamically stable, it is permissible to resume defibrotide at the recommended FDA-approved dose. There is no dose reduction for patients who have a first bleed. However, if someone has a recurrent bleed, the recommendation is to permanently discontinue the therapy.

How does one pursue the administration of defibrotide in someone who requires an invasive procedure, such as a line placement or an LP, or a biopsy, for example? Well, the recommendation is to discontinue the drug for at least 2 hours before the procedure and then resume after the procedure, as long as there is no bleeding observed.

## Charting the Economic/Medical Burden of VOD/SOS[1]

**A Retrospective Cohort Study Using Premier Healthcare Database: Assessing Utilization and Costs of VOD/SOS in HSCT Patients (N = 5,418) Over a 5-Year Period (2009-2014)**

| Criteria | VOD cohort (n = 291) | non-VOD cohort (n = 5,127) | *P* |
|---|---|---|---|
| **Median hospital costs, $** | 119,594 | 62,747 | < .001 |
| **Median length of stay, days** | 28 | 21 | |

- Adjusted hospital costs $8,988 and $41,703 higher in VOD and sVOD groups vs non-VOD group (*P* = .037 and *P* < .001, respectively).
- sVOD group had higher inpatient mortality compared with non-VOD group (Adjusted OR = 5.88, *P* < .001).

1. Dvorak CC et al. 2016 Bone and Marrow Transplant Tandem Meeting (BMT Tandem 2016). Abstract 398.

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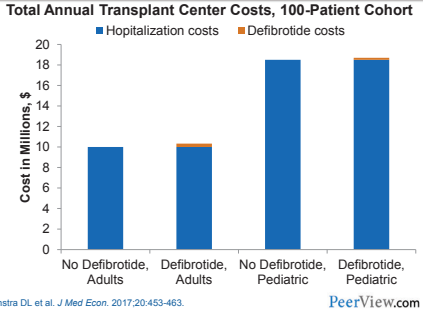
Now, of course, with many of the novel agents that have recently been FDA approved for the treatment of various oncologic and hematologic disorders or supportive care agents for various hematologic/oncologic disorders, it is important to discuss cost, as many of these drugs come with a high price tag. And so, before we delve into the cost of a defibrotide and whether it is a cost-effective agent, or if there is an argument to be made for a cost-effective nature of defibrotide in patients with severe VOD, I did want to just briefly review data that were presented at the Tandem meetings last year, which was a retrospective cohort study using the Premier Healthcare database that assessed utilization and cost of VOD in over 5,000 transplant recipients over a 5-year period.

And what this retrospective cohort study showed was that the median hospital costs for patients who develop VOD is nearly twofold greater compared with those who do not develop VOD. And patients who develop VOD also have about a week longer median length of stay compared with those who do not develop VOD, and thus, contributing to the increased hospital costs.

## Pharmacoeconomic Analysis of Defibrotide: Transplant Center Costs

- Budget impact model analysis of DF based on data reported in phase 3 trial[1]
- Defibrotide associated with relatively modest budget impact compared with overall cost of transplantation[2]
- Defibrotide provides an important survival advantage for VOD with MOD[2]; quality adjusted life-years gained lead to defibrotide being highly cost effective




1. Richardson PG et al. *Blood*. 2016;127:1656-65. 2. Veenstra DL et al. *J Med Econ*. 2017;20:453-463.

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So, how does defibrotide affect the overall cost of the transplant, and what's the financial burden of defibrotide on the transplant center itself? Well, there have been several recent analyses that have looked at the pharmacoeconomics of defibrotide. One was a budget impact model analysis of defibrotide based on data that were reported in the aforementioned phase 3 trial.

What these data showed was that defibrotide was associated with a relatively modest budget impact compared with the overall cost of transplantation. But it is important to note that defibrotide provides a survival advantage in patients with severe VOD that present with either renal or pulmonary involvement.

And so, there are quality-adjusted life-years gained from defibrotide, and thus, it is important to factor in the survival benefit of defibrotide when globally evaluating the pharmacoeconomic impact of this drug on the transplant center, on the overall stem cell transplant course, etc.

## Conclusions

- VOD/SOS remains a potentially life-threatening complication of HSCT
- Pharmacists play an integral role in optimizing multidisciplinary VOD/SOS treatment
- Management of VOD/SOS involves supportive care and defibrotide for severe cases
- Early initiation of defibrotide in severe VOD/SOS is critical for improved outcomes

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In summary, VOD/SOS remains a potentially life-threatening complication of stem cell transplantation. The care of patients undergoing a stem cell transplant involves a multidisciplinary approach to care, which involves physicians, advanced practice providers, nursing staff, and certainly pharmacists, who play an integral role in optimizing the outcomes of stem cell transplant recipients, as well as patients who develop VOD.

Ultimately, the management of VOD/SOS involves supportive care plus/minus defibrotide for severe cases. I think with respect to optimizing outcomes, it's critically important to note that early initiation of defibrotide in patients who develop severe VOD is critical for improved outcomes, as we have rather robust data to show that early initiation of defibrotide therapy for those with severe VOD/SOS, can help improve overall survival.

Thank you for joining me for this educational program.

CPE

# Pharmacy Practice in the Management of VOD/SOS: Developing Optimal Care Models and Modern Therapeutic Arsenals

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