CE/CPE

Practical Approaches to Treating Veno-Occlusive Disease in HSCT Recipients: The Pharmacist's Perspective

Course Director

R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA

Full faculty details inside

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Message From the Course Director

Dear Colleague,

The emergence of veno-occlusive disease (VOD) in the immediate post–hematopoietic stem cell transplant (HSCT) setting is one of the most challenging complications associated with stem cell transplant, leading in serious cases to multiorgan failure (MOF) and death. Effective management of VOD is complex, requiring an accurate assessment for VOD risk factors, consideration of appropriate prophylaxis, a rapid diagnosis when clinical signs develop, and timely treatment selection. The recent FDA approval of defibrotide fills a significant need to treat this rare but frequently fatal complication in patients who receive chemotherapy and HSCT.

In this two-part CE/CPE activity, I review risk factors and preventive and treatment options for VOD in cancer patients receiving HSCT, as well as the role of the pharmacist in coordinating care as they follow the patient throughout their continuum of care. In addition, I focus on appropriate, evidence-based dosing for VOD treatment strategies and potential safety considerations with established and emerging strategies for the management of VOD. I hope you find this educational activity useful in your daily practice.

Sincerely,

R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA

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Practical Approaches to Treating Veno-Occlusive Disease in HSCT Recipients: The Pharmacist's Perspective

VOD/SOS: Disease Features and the Pharmacist's Role in Management

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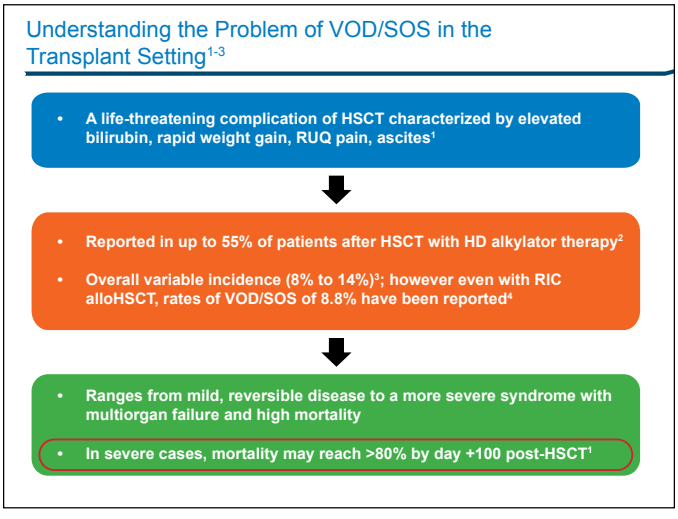
Dr. Harvey: Hello, I'm Donald Harvey from the Winship Cancer Institute of Emory University in Atlanta. I want to welcome you to this educational activity, where we'll explore the role of the oncology pharmacist in the management of veno-occlusive disease or sinusoidal obstruction syndrome, or VOD/SOS, with a focus on the post–stem cell transplant setting. After you complete the activity, access the post-test and evaluation form by clicking the red "Get Certificate" button. I also encourage you to download the slides, the Practice Aids, and any other activity features that may be of interest to you.

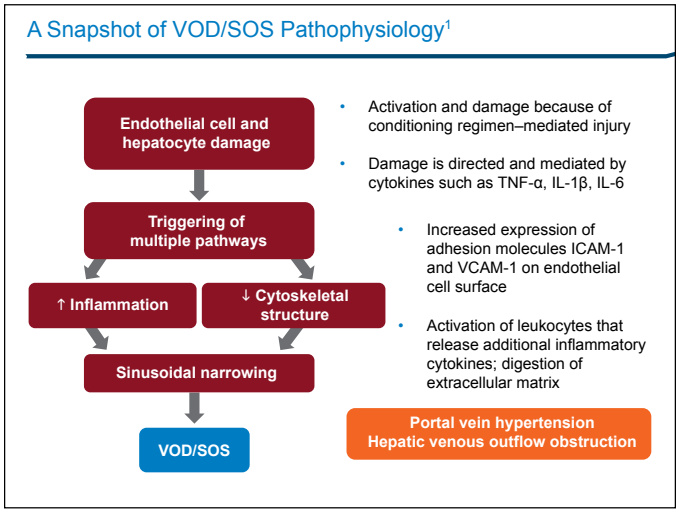


allo: allogeneic; HD: high-dose; HSCT: hematopoietic stem cell transplantation; RIC: reduced-intensity conditioning; RUQ: right upper quadrant; SOS: sinusoidal obstruction syndrome; VOD: veno-occlusive disease.

1. Coppell JA et al. *Biol Blood Marrow Transplant.* 2010;16:157-168.
2. Bearman SI. *Blood.* 1995;85:3005-3020.
3. Carreras E et al. *Biol Blood Marrow Transplant.* 2011;17:1713-1720.
4. Tsirigotis PD et al. *Bone Marrow Transplant.* 2014;49:1389-1392.

So as we think about the problem of VOD or SOS in the transplant setting, it's really a multifactorial but clearly life-threatening complication of transplant. It's characterized by elevations in specifically the bilirubin values, rapid weight gain, right upper quadrant pain, and, in its most advanced form, ascites. It can be seen in up to 55% of patients that undergo conditioning regimens with high doses of alkylator therapy, most commonly busulfan, but it may actually be seen with other alkylators in the transplant setting.

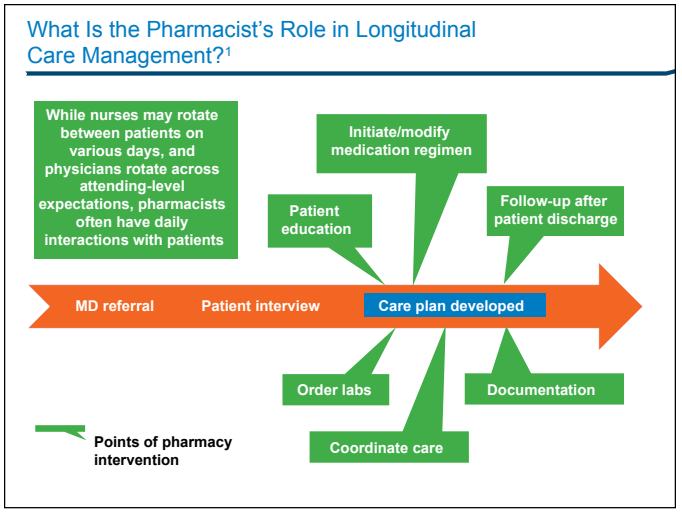
Overall, the incidence is somewhat variable. But even with reduced intensity conditionings in the allotransplant setting, the rates of VOD have been 8.8% and in some cases slightly higher, depending on the series and the type of conditioning. Particularly in severe cases, mortality may be as many as eight of ten patients up to day 100 posttransplant. So it's something that we need to be thoughtful of and mindful of as we evaluate patients following conditioning regimens



ICAM: intercellular adhesion molecule; IL: interleukin; VCAM: vascular cell adhesion molecule.

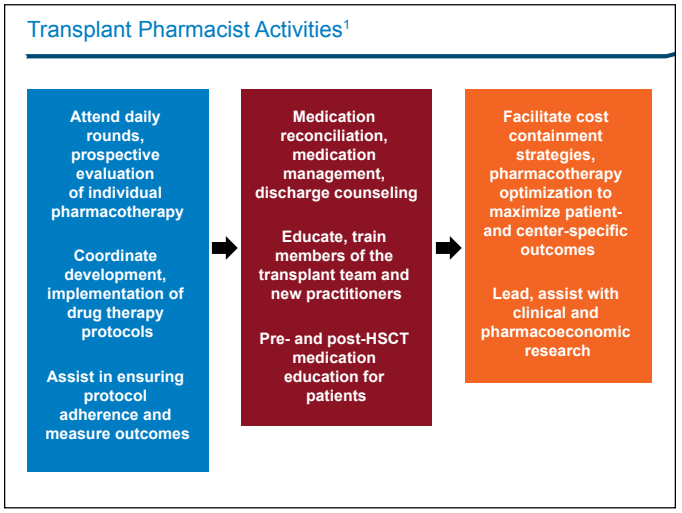
1. Richardson PG et al. *Expert Opin Drug Saf.* 2013;12:123-136.

The pathophysiology of VOD is listed here in this slide. Initially alkylator agents and others may cause endothelial cell and hepatocyte damage. That can then trigger a cascade of effects that leads to inflammatory mediators in certain cytokines, such as TNF-alpha, IL-1 beta, and IL-6. And you can start to decrease the overall structure of the hepatocyte and cytoskeletal structure that can then lead to a narrowing within the liver and then lead to eventual clinical ramifications of VOD and SOS. And there are certain adhesion molecules on the endothelial cell surface that can mediate some of this as well. Overall, clinically you can see portal vein hypertension, and really a reduced hepatic venous outflow is what begins the clinical manifestations of VOD and SOS.



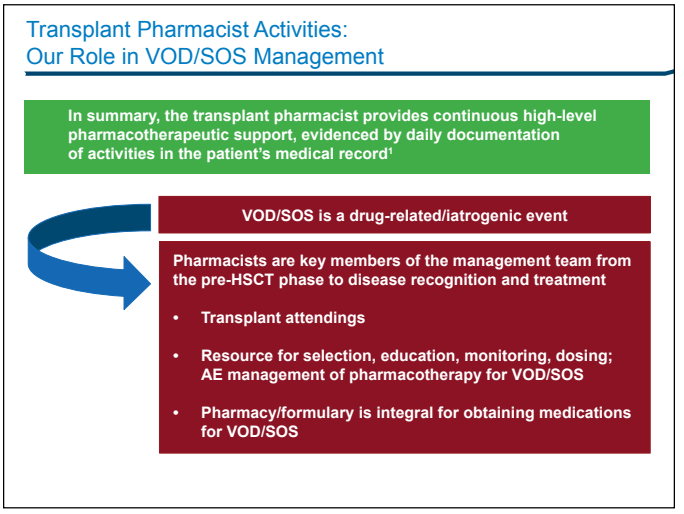
1. www.accp.com/docs/positions/misc/JCPP_Pharmacists_Patient_Care_Process.pdf. Accessed April 5, 2016.

In general when we think about pharmacists' role across cancer, there are a variety of things that can be done by us and are probably best done, candidly, by us in terms of patient education and drug therapy. When we think specifically within the transplant process, one example is the management of patients on calcineurin inhibitors and other graft-versus-host disease prophylaxis measures. And so thinking about therapeutic concentrations, ensuring patients have access to the drug, ensuring that they know what side effects to consider and when to bring on a provider for help with their management are all things that we can do quite well in terms of drug management within the transplant setting and others. And overall, it's important that we look at all aspects of the care of patients undergoing transplant and what our role can be within their care.



1. Allowaya RR et al. *Am J Transplant*. 2011;11:1576-1583.

Again, specifically within transplant, many of us in the profession attend rounds, coordinate development of a variety of therapy protocols that are driven by data. Things like febrile neutropenia management and other infectious disease approaches to the care of the patient are certainly in the pharmacist's wheelhouse. Thinking about management and counseling, educating and training team members, including other advanced practice providers, new practitioners—education of patients before the transplant, during the transplant, and certainly at discharge is all important. And then finally our overall role within being good drug stewards in institutions and in care and thinking about how we can maximize outcomes and certainly help with maximizing the value that we spend on patients undergoing the transplant procedure, all while trying to really ensure that patients get the best therapy possible.



1. Allowaya RR et al. *Am J Transplant*. 2011;11:1576-1583.

So thinking specifically about our role in VOD and SOS, it can be quite a difficult thing to tease out when patients present with perhaps a slightly elevated weight or an elevated bilirubin, which may be multifactorial. And so because it is a drug-related and drug-induced event, I think we are certainly central to how patients can be recognized and hopefully managed well. Overall, we're key members of the team, again, to our attending colleagues, to fellows, and others in thinking about how we can manage patients with VOD and thinking about drugs that we might consider for additional management of VOD that may come down the pipeline.

VOD/SOS: Risk Factor Summary[1]

Patient- and Disease-Related Factors	
Age	Children or elderly > adolescent/adult
Health status	Comorbidities and poor performance status > normal
Diagnosis	Specific malignancies/high-risk conditions[a] > malignancy > non-malignancy
Status of the disease	Advanced > remissions
Liver status	Hepatitis, iron overload, fibrosis, cirrhosis > normal
Previous liver disease	Yes > no
Previous drugs	Gemtuzumab ozogamicin • Be vigilant: newer antibody–drug conjugates (eg, inotuzumab in ALL) may be associated with high risk for VOD[2]

[a] Hemophagocytic lymphohistiocytosis, adrenoleukodystrophy, osteopetrosis, thalassemia (benign but higher risk).

ALL: acute lymphoblastic leukemia.

1. Carreras E. *Br J Haematol*. 2015;168:481-491.
2. Kebriaei P et al. *Clin Lymphoma Myeloma Leuk*. 2013;13:296-301.

So in summary, in looking at patients undergoing conditioning and considering risk factors for the development of VOD, there are a few things here that I think are important. Those who are very young or very old tend to be at a greater risk than those in the middle, and particularly those that have comorbidities and those who might have a poor performance status at the time of transplant. Optimally we're not taking those patients to transplant, but there may be interim things that occur that can lead to an increased risk.

The diagnosis of specific cancers and high-risk conditions can be problematic. If you have an advanced disease, if you come into transplant with more active cancer, then you're also at greater risk. And certainly the status of the liver, patients who have been transfused heavily may have iron overload. Anyone who has a preceding liver disease for other reasons are certainly all going to be at risk more than patients with normal function.

And then certainly drugs that patients may have gotten. We know that the use of gemtuzumab ozogamicin was associated with an increased risk of VOD following conditioning with busulfan in patients with AML, and it might also be possible that other antibody drug conjugates are possibly related and may increase risk as well.

VOD/SOS: Risk Factor Summary (Cont'd)[1]

Transplant-Related Factors	
Type of HSCT	Allogeneic > syngeneic/autologous
Grade of compatibility	Major-mismatch > minor-mismatch > match
Origin of stem cells	Bone marrow/T-cell depleted (TCD) > non TCD > peripheral blood
Conditioning regimen	
Total dose	MAC > RIC
Busulfan	Oral non-adjusted > oral-dose targeted > IV
Order of administration	Bu + Cy > Cy + Bu
GVHD prophylaxis	Calcineurin inhibitors (CNI) + sirolimus > with CNI > without CNI
Other hepatotoxic drugs	Yes > no
HSCT number	Second > first

Bu: busulfan; Cy: cyclophosphamide; GVHD: graft-versus-host disease; MAC: myeloablative conditioning.

1. Carreras E. *Br J Haematol*. 2015;168:481-491.

Continuing risk factors for VOD and SOS, certainly the type of transplant matters. Patients who have an allogeneic transplant are at a greater risk. Compatibility of the graft with the patient, and so a greater mismatch, increases the risk of the development of VOD as well.

And the conditioning regimen is, of course, the integral part to this. And so full doses of conditioning regimens are at greater risk of causing VOD than reduced intensity. Busulfan specifically is important in that the highest risk is with oral busulfan that's not PK-adjusted for area under the curve. Patients who receive busulfan prior to cyclophosphamide are at greater risk than those patients who receive cyclophosphamide first, followed by busulfan.

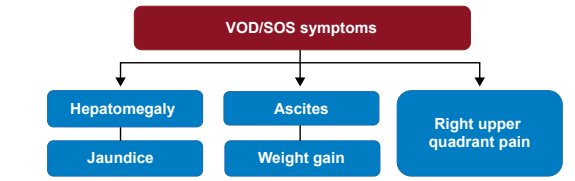
Thinking about graft-versus-host disease prophylaxis as well, more intensive prophylactic regimens tend to be associated with a greater risk of VOD compared to less intensive regimens, and that goes along with the origin of stem cell data as well.

VOD/SOS Prophylaxis at a Glance[1,2]

Drug	Comments
Anticoagulants (heparin sodium, LMWH)[1]	Inconclusive results, infusion difficult (sodium heparin), hemorrhagic risk
Antithrombin concentrate[1]	Lack of efficacy
Prostaglandin E1[1]	Lack of efficacy, inconclusive results
Pentoxifylline[1]	Lack of efficacy, ↑ VOD/SOS
Ursodiol[1,2]	Mixed results (less liver toxicity, GVHD, and better survival, but no overall reduction in VOD incidence)
Defibrotide[2,3]	Lower incidence of VOD/SOS, VOD with renal failure, and GVHD in randomized study; *P* = .05, .02, and .005, respectively[3]

No agents approved for prophylaxis in United States; ursodiol, defibrotide among the options included in European guidelines for VOD prevention[2]

VOD/SOS Symptoms and Laboratory Findings[1]



Laboratory Findings	Clinical Notes
Elevated aminotransferases	• The triad of **weight gain (usually from ascites), elevated bilirubin, and RUQ pain or hepatomegaly** is common in severe VOD • VOD u**sually occurs within a month of transplant, but can develop much later** (approaching day +100 post-HSCT)
Hyperbilirubinemia (conjugated)	
Prolonged PT	
Signs of decreased synthetic function (low albumin)	

LMWH: low molecular weight heparin.

1. Carreras E. *Br J Haematol*. 2015;168:481-491.
2. Dignan FL et al. *Br J Haematol*. 2013;163:444-457.
3. Corbacioglu S et al. *Lancet*. 2012;379:1301-1309.

So thinking about prophylaxis and thinking about specifically low-dose heparin continuous infusion, it's problematic. It ties up a line in patients who may need that line for other things. Certainly our nursing colleagues prefer to keep lines free as much as possible.

They also may have hemorrhagic risk. Antithrombin really has been suboptimal in terms of efficacy. And other agents listed here—prostaglandin, pentoxifylline, ursodiol—have all had sort of mixed results in the past.

Looking specifically at defibrotide, there has been a lower incidence of VOD and SOS and certainly VOD with renal failure in a randomized study. And these are statistically significant differences in the use of defibrotide versus the control arm.

And again, so there are no currently approved agents in the US, but in the European guidelines both ursodiol and defibrotide are among options in VOD prevention. But it's my opinion that ursodiol really doesn't do a whole lot to the underlying pathophysiologic process, but rather probably just treats the bilirubin number.

PT: prothrombin time.

1. Chao N. *Blood*. 2014;123:4023-4026.

There are many things that can happen in patients who begin to develop VOD. Hepatomegaly can be a sign relatively early, and so abdominal exams can be helpful there. Ascites and weight gain can occur as well. Ascites a little bit later, but any time patients begin to gain weight in that peritransplant period you need to think about it.

Jaundice is a late event as well. And right upper quadrant pain may also be there. But really some of the earliest findings tend to be those laboratory findings of transaminitis. And certainly the hallmark is hyperbilirubinemia, and specifically conjugated bilirubin.

You may also see prolonged PTs that don't get better. And over time you can see decreased synthetic function, low albumin. But typically weight gain, elevated bilirubin are the earliest things that we begin to see. VOD can occur in a later timeframe, but usually it's within a month of transplant, again reflecting the idea that the conditioning regimen is the etiology that causes this.

Diagnostic Imaging: Ultrasound

Ultrasound may be helpful in the exclusion of other disorders in patients with suspected VOD[a]

Findings that may suggest VOD/SOS[1-3]

- Ascites
- Reversal of flow in the portal veins
- Hepatic artery resistance index: 0.75
- Abnormal portal vein waveform

[a] Doppler ultrasonography may also have prognostic significance for VOD severity.[4]

1. Chao N. *Blood*. 2014;123:4023-4026.
2. Sharafuddin MJ et al. *J Ultrasound Med.* 1997;16:575-586.
3. Carreras E. *Br J Haematol*. 2015;168:481-491.
4. Lassau N et al. *Transplantation*. 2002;74:60-66.

For imaging, ultrasound may be helpful, but really it's helpful to exclude other things. When we think about elevated bilirubins, they may occur secondary to hemolysis or other drugs, for example. But thinking about that and using ultrasound, other things may be added to our understanding and diagnostic differentiation. And so things like reversible flow in the portal veins, some of the arterial resistance in the liver, as well as portal vein wave form may also suggest VOD. And so ultrasonography may actually help in many instances to differentiate VOD from other causes of hyperbilirubinemia and potentially weight gain.

Diagnostic Criteria for VOD[1-4]

Modified Seattle Criteria[2]	Baltimore Criteria[3]
Two of the following criteria must be present within 20 days of transplant	**Bilirubin must be >34.2 µmol/L (2 mg/dL) within 21 days of transplant *and* two of the following criteria must be present**
❑ Bilirubin >34.2 µmol/L (2 mg/dL)	❑ Hepatomegaly
❑ Hepatomegaly or right upper quadrant pain	❑ Ascites
❑ Weight gain (>2% from pretransplant weight)	❑ Weight gain (>5% from pretransplant weight)

Criteria have high specificity of 91% to 92%, but less sensitivity[4]

1. McDonald GB et al. *Hepatology*. 1984;4:116-122.
2. Shulman HM, Hinterberger W. *Bone Marrow Transplant.* 1992;10:197-214.
3. Jones RJ et al. *Transplantation*. 1987;44:778-783.
4. Carreras E et al. *Ann Hematol*. 1993;66:77-80.

There are two main groups that have developed diagnostic criteria for VOD, including the group at Seattle and the group in Baltimore at Hopkins. And looking at the Seattle Criteria, they originally came out in the '80s but then were updated and modified in the early '90s, showing that two of the following criteria had to be present within 20 days of the transplant. Specifically, a bilirubin above 2, hepatomegaly or right upper quadrant pain and then weight gain, which had to be greater than 2% from the pretransplant or admission weight.

The Baltimore Criteria also described bilirubin above 2 mg/dL there within 3 weeks of transplant, but also require that two of the following criteria be present, including hepatomegaly, ascites, and, again, weight gain, although in this instance more than 5% from pretransplant weight. So these criteria have certainly a very high specificity for VOD, but they're really not particularly sensitive to identify VOD early. And so that's an important point as we think about the role of the pharmacist in the patient management and assessment within VOD.

Some VOD/SOS Presentations Not Captured Using Current Criteria

Examples	Comments
Lack of elevated bilirubin[1]	• In some cases bilirubin was <2 mg/dL and reversal of portal venous flow was evidenced by ultrasound[1]
Late-onset VOD/SOS[2,3]	• May develop >30 days after transplant • Not accounted for in Baltimore/Seattle Criteria • May be under-recognized in patients undergoing transplant; should be considered in the differential diagnosis, particularly after high-dose busulfan

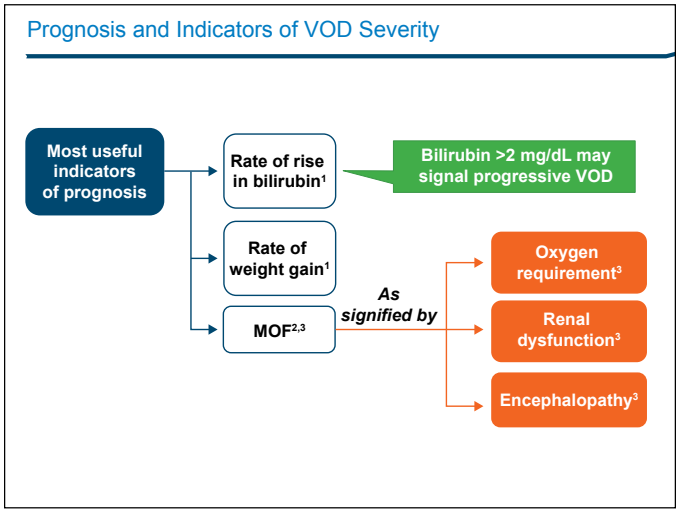
In these cases, waiting for all criteria to appear may delay therapy; early ultrasound evaluation may lead to a more timely diagnosis and earlier therapeutic intervention

1. Myers KC et al. *Biol Blood Marrow Transplant*. 2015;21:379-381.
2. Pai RK et al. *Leuk Lymphoma.* 2012;53:1552-1557.
3. Shah MS et al. *J Cancer Res Ther.* 2009;5:312-314.

So there are patients who won't have an elevated bilirubin. And that's somewhat rare, but you may have bilirubin that's less than 2 mg/dL. But if you have concurrent radiographic findings by ultrasonography that suggest VOD and evolving VOD, then that lack of elevated bilirubin should not make you say that, well, the patient just doesn't have this.

Similarly, late-onset VOD, and so those patients that may have for various reasons VOD that begins or begins to clinically manifest more than 30 days after transplant, those patients may be there. And again, those patients getting high-dose busulfan and have a greater-than-30-day after transplant process presentation.

If you wait for all the criteria to appear, then active interventions may be delayed. So early recognition of VOD is certainly critical, and the use of ultrasound can help to make that happen.



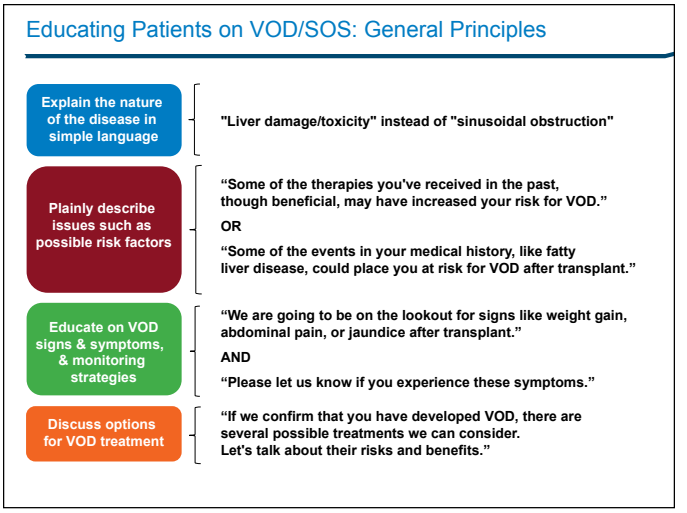
MOF: multiorgan failure.

1. Bearman SI et al. *J Clin Oncol.* 1993;11:1729-1736.
2. Coppell JA et al. *Biol Blood Marrow Transplant.* 2010;16:157-168.
3. Lee SH et al. *Bone Marrow Transplant.* 2010;45:1287-1293.

The predictors of severity are listed on this slide. Some of the most useful indicators really are the rate of rise. And so if on day plus 8 you have a certain bilirubin value, day plus 9 it's double that, day plus 10 it's double that, then that is really certainly a harbinger of VOD evolving and is something that needs to be very aggressively intervened upon.

The rate of weight gain is similar, and so anytime these items occur in a daily fashion. And sometimes twice-daily weights are gotten in patients at certain centers to try to understand rates of weight gain.

And then finally multiorgan failure, which certainly has a harbinger of a bad outcome for many things, not just VOD. But signified by, again, O2 requirements, elevated creatinine, and the beginnings of neurological decline. And when patients reach that point, outcomes are quite poor.



So if we're talking to patients about the risk of VOD within the transplant process, it's important to do a number of things. Certainly they won't know what VOD or SOS means, so the idea of liver damage or liver toxicity maybe is going to be much more helpful.

Describe plainly some risk factors, and so talking to patients and saying, "Because you've had so many transfusions, the iron in those blood cells tends to get dumped into the liver or live in the liver, and so that may cause you to be at risk for liver damage from our chemotherapy." But it's important to also let them know that there is a reason we're doing the transplant and to balance the risk versus benefit.

Educate patients on signs and symptoms. If they look at their weight and they say, "Hey, you know, that's much higher than it was yesterday, and I usually don't weigh that much. And I haven't eaten a whole lot because I'm nauseated," then that should signal to them as well that there might be issues to consider.

Then talk as well about what we can do for them. Certainly patients want to be educated and understand that they may have options if this should occur. And so saying things like, "If we confirm that you have developed VOD, then there are some possible treatments we can consider, and we'll talk about them now."

Treating VOD/SOS: A Pharmacy Perspective

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VOD/SOS Associated With Economic Costs[1]

A retrospective cohort study using a Premier Healthcare database assessed utilization and costs of VOD in HSCT patients (N = 5,418) over a 5-year period (2009 to 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)

HSCT: hematopoietic stem cell transplantation; SOS: sinusoidal obstruction syndrome; sVOD: severe VOD; VOD: veno-occlusive disease.

1. Dvorak CC et al. Annual Meeting of Center for International Blood & Marrow Transplant Research (CIBMTR) and the American Society of Blood and Marrow Transplantation (ASBMT) 2016 (BMT Tandem 2016). Abstract 398.

Dr. Harvey: So in terms of thinking about our profession's perspective on treating VOD, it's important to think about how we can consider drugs and consider agents used in transplant and how they may offset costs or incur subsequent costs. And so this was a retrospective data analysis using a Premier Healthcare database looking at VOD specifically in our transplant patients, over 5,000 transplant patients over a 5-year period in a relatively recent look. And when you looked at patients that developed VOD, the cost of their hospitalization was double.

In thinking about that, you can certainly see that patients may have intensive care unit stays. Their length of stay is certainly longer. The complications associated with alternate organ dysfunction, additional organ dysfunction can be there. They were in-house a week longer but probably more interventions and potentially intensive care units were part of this group. And so, again, overall the patients with VOD and suspected VOD had much higher costs but also had a higher mortality compared to those who didn't have VOD.

Role of Pharmacist in Influencing Optimal Prescribing

Drive use of most cost-effective therapies

Weighing risks and benefits of pharmacotherapy

In VOD/SOS, can LOS and hospital costs be reduced?

Preferred Drug Formulary

- **Pharmacists educate physicians' staff on optimal prescribing[1]**
- **Provide decision support tools[1]**
  - **Clinical evidence summaries**
  - **Dosing conversion guides**

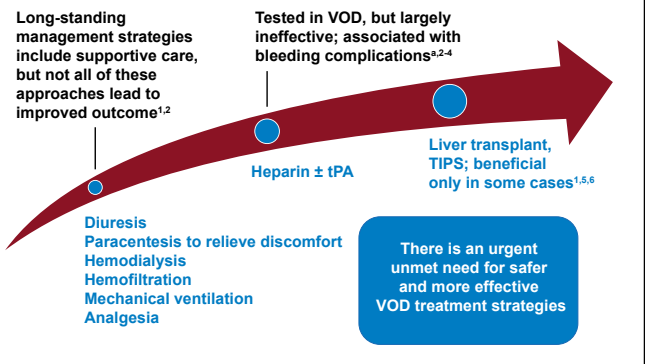
LOS: length of stay.

1. Allowaya RR et al. *Am J Transplant*. 2011;11:1576-1583.

So how can we as pharmacists influence prescribing in patients undergoing transplant? Well, in general and certainly in today's climate thinking about cost-effectiveness. We have to remember the effectiveness side of this equation. So using subtherapeutic doses of expensive drugs or avoiding drugs that are costly just for the sake of avoiding them really doesn't help anyone. Most importantly, it doesn't help the patient.

So thinking about risks and benefits and thinking about other things, like hospital stay, can help pharmacists when considering what should be on the formulary and what we may be able to provide patients, both in the hospital and then outside of the hospital. We can also help to provide some decision tools, including laboratory values that might come together in a certain way or evidence summaries and thinking about conversions of IV to PO and those sorts of things. So these are all ways that we may influence optimal prescribing, in addition to others.

Traditional Management of VOD/SOS Points to a Need for More Effective Treatment



[a] Not recommended in VOD with MOF; avoid in pulmonary, renal failure cases.

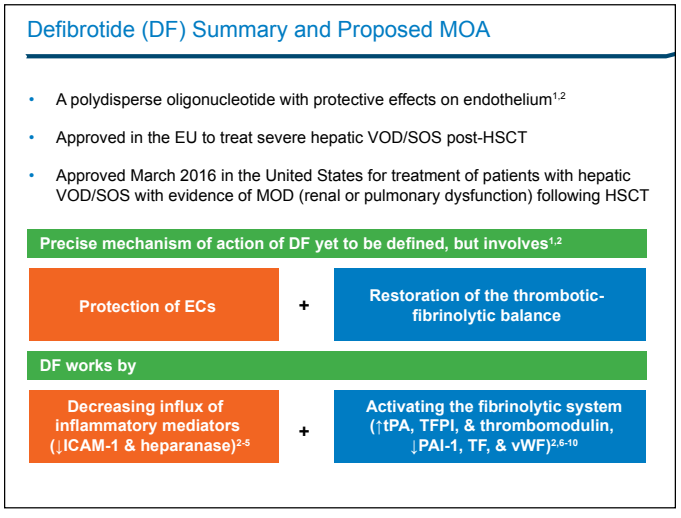
MOF: multiorgan failure; TIPS: transjugular intrahepatic portosystemic shunt; tPA: tissue plasminogen activator.

1. DeLeve LD et al. *Hepatology*. 2009;49:1729-1764.
2. Helmy A et al. *Aliment Pharmacol Ther.* 2006;23:11-25.
3. Bearman SI et al. *Blood*. 1997;89:1501-1506.
4. Schriber J et al. *Bone Marrow Transplant.* 1999;24:1311-1314.
5. Richardson P, Guinan E. *Acta Haematol*. 2001;106:57-68.
6. Azoulay D et al. *Bone Marrow Transplant.* 2000;25:987-992.

So traditional management of VOD has been suboptimal, and we need better therapies overall for management of VOD in those patients where it happens. So supportive care occasionally can lead to improved outcome. And those are things like diuresis to try to remove the ascites. But one has to be concerned about, again, renal dysfunction secondary to that, and renal dysfunction may evolve because of VOD. Again, moving patients to the ICU, thinking about hemodialysis when needed if patients undergo renal failure. And then finally, other procedures that may be used in additional management of pain, for example.

Heparin plus or minus TPA have been tested, but I think many clinicians are fearful of the bleeding risk associated with heparin, even low-dose heparin. And similarly are a little bit concerned about the efficacy of that. And so in patients that have thrombocytopenia following transplant, using TPA makes many people quite nervous and concerned.

And then very rarely liver transplant or TIPS has been done, and is really not particularly beneficial in most instances. So thinking about more effective strategies is pretty important.



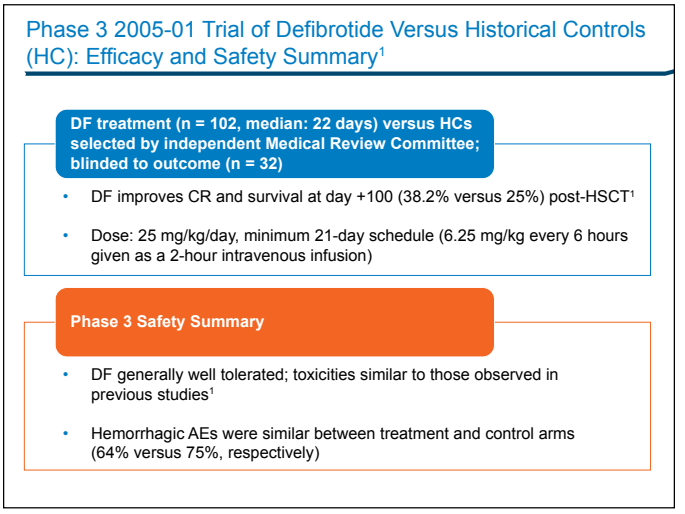
EC: endothelial cells; ICAM: intercellular adhesion molecule; PAI: plasminogen activator inhibitor; TF: tissue factor; TFPI: TF pathway inhibitor; vWF: von Willebrand factor.

1. Richardson PG et al. *Expert Opin Drug Saf.* 2012;12:123-136.
2. Guglielmelli T et al. *Expert Opin Biol Ther.* 2012;12:353-361.
3. Pellegatta F et al. *Br J Pharmacol.* 1996;118:471-476.
4. Echart C et al. *Bone Marrow Transplant.* 2010;45(Suppl 2):s281.
5. Ostrovsky O et al. *Blood*. 2010;115:2319-2328.
6. Falanga A et al. *Leukemia*. 2003;17:1636-1642.
7. Morabito F et al. *Expert Opin Biol Ther.* 2009;9:763-772.
8. Palomo M et al. *Biol Blood Marrow Transplant.* 2011;17:497-506.
9. Zhou Q et al. *Thromb Hemost*. 1994;71:507-510.
10. Cella G et al. *Clin Appl Thromb Hemost*. 2001;7:225-228.

So thinking about defibrotide, it's a relatively small molecular weight oligonucleotide with protective effects on the endothelium. It's been approved in the EU to treat severe hepatic VOD posttransplant. In the US it was approved in March 2016 for the treatment of patients with hepatic VOD or SOS with evidence of multiorgan dysfunction following stem cell transplant.

Again, the precise mechanism is yet to be defined, but it may involve protection of these endothelial cells from initial damage and then restoration of a balance between thrombotic and fibrinolytic mechanisms. As a reminder, the thrombotic balance is tilted towards thrombosis within VOD, and fibrinolysis is impaired, and so clot formation within the sinusoidal space could happen.

It probably works by decreasing influx of those mediators, so adhesion molecules and heparanase. And then endogenously activating the fibrinolytic system—these are all proteins that increase the breakdown of clots, including thrombomodulin and tissue plasminogen activator, but also decreasing those antifibrinolytic proteins that are listed here as well.



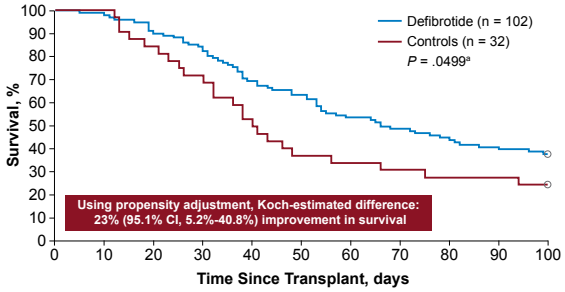
CR: complete response.

1. Richardson PG et al. *Blood.* 2016 Jan 29. [Epub ahead of print.]

So the phase 3 study of defibrotide versus historical controls is listed here. And so overall this analysis showed that defibrotide improved the complete response and survival at day 100 posttransplant. And the dose is listed here of 25 mg/kg/day on a 21-day schedule, or longer schedule.

The safety summary was that overall it's well tolerated. And previous studies, there are adverse events that have been shown, some hemorrhagic adverse events, but they were somewhat similar between the treatment and control arm, at 64[%] and 75%.

2005-01: Survival Up to Day +100[1]



[a] Unadjusted log-rank *P*.

1. Richardson PG et al. 56th American Society of Hematology Annual Meeting (ASH 2015). Abstract 737.

Specifically here looking at the Kaplan-Meier survival curve at day 100, patients who received defibrotide compared to controls, there was a statistically significant difference between the groups. Defibrotide—102 patients again and 32 controls—showing that the median overall survival was improved at propensity adjustment looking at 23% in patients who received defibrotide versus those who received control or standard-of-care regimens.

Update From Treatment IND: Summary of Adverse Events[1]

- After defibrotide treatment for a median of 21 days, tolerability and low rate of DF-associated toxicities consistent with prior studies[2,3]
- Hypotension was most common; reported in <15% of patients[1]

Category, n (%)	Safety (n = 649)	HSCT Only (n = 579)
≥1 AE	446 (69)	401 (69)
≥1 grade 3/4/5 AE	359 (55)	330 (57)
≥1 AE leading to discontinuation	181 (28)	170 (29)
≥1 treatment-related AE[a]	139 (21)	125 (22)

[a] Considered to be possibly, probably, or definitely related to defibrotide. Missing relationships were analyzed as "possibly related."

IND: investigational new drug.

1. Richardson PG et al. 47th Congress of the International Society of Paediatric Oncology (SIOP 2015). Abstract 0-009.
2. Richardson P et al. *Blood*. 2009;114:Abstract 654.
3. Richardson P et al. *Biol Blood Marrow Transplant*. 2010;16:1005-1017.

From the treatment IND, in those patients that have been enrolled, this is an analysis of those who have gotten compassionate use defibrotide. Inclusion was either by clinical diagnosis or the original severe VOD patients by the Baltimore Criteria posttransplant and then an amendment that also included non-severe VOD in those patients who did not have multiorgan dysfunction and by modified Seattle Criteria. And that was either post–stem cell transplant or in patients not undergoing transplant, those who might have gotten chemotherapy that had been associated with VOD.

So looking at adverse events here, again the transplant-only group we certainly can appreciate that transplant has its own set of adverse events. If there was ≥1 grade 3, 4, 5 adverse event, those numbers were similar between the two analyses. And the most common adverse event between any of these was hypotension in patients that had gotten defibrotide, but it was in less than 15% of people.

Survival at Day +100: All HSCT Patients and Subgroups[1]

Subgroup	Day +100 Survival, n/N (%)
All HSCT patients	288/573 (50)
VOD/SOS with MOD	159/351 (45)
All allografts	248/503 (49)
Allografts with MOD	140/317 (44)
Allografts without MOD	108/186 (58)
All autografts	40/68 (59)
Autografts with MOD	19/34 (56)
Autografts without MOD	21/34 (62)

1. Richardson PG et al. SIOP 2015. Abstract 0-009.

When we think about day 100 survival in those who have VOD with multiorgan dysfunction failure, it was 45%. Allografts were 49%. And those with and without multiorgan dysfunction are listed there. And certainly when patients progressed to multiorgan dysfunction, their survival is reduced.

And autograft data, you can see here 59% for all. But again, those with multiorgan dysfunction was slightly lower than those without. So the biggest risk certainly is allografting, and certainly allografting with the development of multiorgan dysfunction has the worst outcome.

Treatment IND: The Effect of Early Treatment With Defibrotide on Complete Response and Survival[1,2]

In a population-wide analysis of treatment initiation before or after days 0, 1, 2, 3, 4, 5, 6, 7, and 14, earlier initiation of DF was associated with higher survival rates

- Significant for all cut-points assessed except day 14 ($P \leq .045$); echoes earlier evidence suggesting treatment within 2 days of diagnosis associated with better outcome[1,2]
- For the subgroup of patients with MOD, day +100 survival differences ranged from 12.8% to 25.6% and were statistically significant ($P \leq .021$) at all cut-points except day 14[1]

1. Richardson PG et al. ASH 2015. Abstract 4311.
2. Richardson PG et al. ASH 2013. Abstract 700.

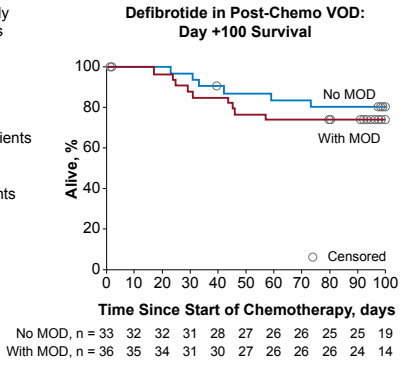
And so the treatment IND and the early treatment on complete response and survival analysis of initiation is important because, again, early recognition of this disorder is critical to improving outcomes no matter what the intervention. But earlier initiation of a drug when it is recognized is generally better than not.

And so looking at the cut-points, except for day 14 it suggests that treatment within 2 days of diagnosis is associated with better outcome. So that's important as we think about when patients get conditioning, when they may develop VOD. If it's over a weekend, for example, then it's important to initiate therapy quickly. And certainly within 2 days appears to have a better outcome with defibrotide management.

For the subgroup analysis of patients with multiorgan dysfunction, day 100 survival differences ranged from about 13% to about 26%, more significant at all cut-points again except day 14. So showing that earlier initiation is improved.

Further Insight From Treatment IND: VOD/SOS After Chemotherapy[1]

- Although VOD/SOS is typically associated with HSCT, it does occur in the non-HSCT, post-chemo setting
- In T-IND, 11% (69/642) of patients with post-chemo VOD (likely an underestimate because of exclusion of non-HSCT patients in original protocol)
- 52% with MOD versus 61% in the HSCT population



1. Kernan NA et al. ASH 2015. Abstract 3121.

So VOD typically is associated with transplant, but it does occur in patients who are not undergoing transplant. And this treatment IND, 11% of patients who had received chemotherapy alone without transplant who developed VOD are listed here. And 52% who had multiorgan dysfunction versus 61% in the stem cell population.

So survival again just showing that in those patients who received defibrotide, earlier intervention is better. Certainly intervention prior to the development of multiorgan dysfunction is important.

Conclusions

- Take VOD/SOS seriously as a potentially severe complication in the transplant setting
- Know the risk factors (transplant and pretransplant)
- The pharmacist's role includes
  - Contributing to patient and team education on the signs and clinical symptoms of VOD
  - Development of medication plans as newer therapies are approved in VOD/SOS
- Be familiar with the safety and efficacy profile of novel agents
  - Use of supportive care plus defibrotide emerging as an effective option in VOD/SOS
  - Defibrotide approved for use in post-HSCT patients with VOD/SOS and renal or pulmonary dysfunction

So in conclusion, early recognition and serious recognition of VOD is important in patients undergoing transplants. Knowing the risk factors is critical for patients to help to understand who's at a greater risk and identify and potentially predict who is likely to develop VOD.

And our role as pharmacists is understanding that this is a drug-induced disorder and making sure that our partners on the care team—advanced practice providers, nurses, physicians—understand the signs and clinical symptoms of VOD as it evolves. Thinking as well about medication plans as we consider newer therapies that are approved for use. Increasing our options of prevention and treatment of VOD are important in ensuring that people understand the value of those therapies. And then finally, knowing the safety and efficacy of this and any other novel agents that's out there. Supportive care and defibrotide may be an effective option within these patients who develop VOD.

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