Hepatic veno-occlusive disease (VOD) as a distinct clinical entity was first described in South Africa and was linked to the ingestion of pyrrolizidine alkaloids contained in Senecio tea. The characteristic occlusion of the terminal venules of the liver in the individuals who drank this tea led to the term \textit{veno-occlusive disease}. On the basis of more recent work suggesting that the sinusoidal changes are primary events in the pathology of the disease, the term \textit{sinusoidal obstruction syndrome} may describe the condition better. Several species of plants containing pyrrolizidine alkaloid can cause VOD and have been associated with epidemics of this disease in underdeveloped nations. VOD developing after allogeneic stem cell transplantation was first described in 1979, and stem cell transplantation has since become the most common cause of VOD in the Western Hemisphere. However, VOD also has been described in association with chemotherapeutic agents such as actinomycin D, mithramycin, dacarbazine, cytosine arabinoside, and 6-thioguanine used at conventional doses and with long-term use of the immunosuppressive agent azathioprine. More recently, VOD has been seen after therapy for acute myelogenous leukemia with the monoclonal anti-CD33 antibody gemtuzumab ozogamicin (Mylotarg). The combination of chemotherapy and radiation used in abdominal areas, for example in children with Wilms tumor, has been associated with development of VOD. Also, VOD is seen after liver transplantation.

VOD is a well-recognized complication of hematopoietic cell transplantation, both allogeneic and autologous, and is categorized as a conditioning-related toxicity. The incidence of this condition varies from less than 5% to as high as 70% in different reports, depending on the diagnostic criteria used, the population studied (eg, pediatric vs adult), and the differences in conditioning therapy used. Because VOD contributes to considerable morbidity and mortality among patients undergoing stem cell transplantation, gaining an understanding of its pathogenesis and developing new modalities for its prevention and therapy remain important tasks.

PATHOLOGY
The characteristic histological changes seen in VOD have been studied extensively and are best understood in the setting of normal liver histology. Hepatocytes have a canalicular surface, which forms the bile canaliculi, and a basolateral sinusoidal surface. The sinusoidal surface is lined by a single layer of endothelial cells, the fenestrae of which allow free communication between the sinusoids and the extravascular space of Disse. A delicate network of collagen fibers supports the sinusoidal lining, and there is a scant amount of subendothelial stromal tissue. The hepatic parenchyma is organized classically into lobules based primarily on the vascular architecture. Each lobule is arranged...
around a hepatic venule, and the portal triad containing the bile ductule, portal venule, and hepatic arterioles forms the corners of the hexagonal lobule, defining a functional and circulatory compartment of the liver. The zone around the portal triad has a rich vascular supply from the portal venous system and defines the periportal zone. The central region of the lobule close to the hepatic venules forms the centrilobular zone. The sinusoids form the venous conduits for the flow from the portal vein to the hepatic venules.

Endothelial injury seems to be the initiating event in the cascade of events leading to the hepatic changes and clinical manifestation of VOD. A rat model of hepatic VOD has been described that has contributed much to our understanding of events that lead to the development of the histological changes. In this model, the hepatic injury is initiated by treatment with a pyrrolizidine alkaloid extracted from the plant genus *Crotalaria* and leads to manifestations similar to those seen clinically, including hyperbilirubinemia, ascites, and hepatomegaly. In this model, the earliest changes after alkaloid ingestion appear in the sinusoids. This leads to the loss of the endothelial cell fenestrations and the appearance of gaps in the lining, which is followed by extravasation of red cells into the space of Disse. Sinusoidal endothelial cells are injured extensively, resulting in widespread denudation of the sinusoidal lining.

In the early stages of VOD, histological examination findings show thickening of the subintimal zone of the central and sublobular venules due to edema. Immunohistochemical studies have shown the presence of fibrin and factor VIII in the intramural and periadventitial portions of the venular walls. Also present in the subendothelial region are red blood cell fragments, but no platelet fragments have been shown. No inflammatory infiltrate is identified in the tissue sections. The subintimal thickening leads to narrowing of the venular lumen and increased resistance to blood flow through the venules and contributes to the hemodynamic changes seen in this disease. The decreased venous outflow leads to severe hepatic congestion and sinusoidal dilatation, appreciated on the histological examination, and portal hypertension characteristic of VOD.

Accompanying these changes in the vascular bed is evidence of hepatocyte injury and death, and these changes appear to be primarily localized to the centrilobular region of the liver. The low-flow state induced by the sinusoidal obstruction results in considerable heterogeneity in sinusoidal blood flow and redistribution of hepatic microcirculation. These changes can result in focal ischemia and progressive microvascular, parenchymal, and Kupffer cell phagocytic derangements in the liver. Mediators such as 5-hydroxytryptamine (5-HT), prostaglandins (PGs), leukotrienes, and free radicals released by platelets, Kupffer cells, leukocytes, and mast cells may play a role in the endothelial damage and the downstream events leading to hepatocellular ischemia and injury. Shulman et al correlated the histological findings in VOD, including frequency of hepatic venular occlusion, degree of occlusion, eccentric luminal narrowing, centrilobular sinusoidal fibrosis, and hepatocyte necrosis. This study showed that involvement of the hepatic venules was not an essential feature of the disease, consistent with the concept that the primary obstruction occurs in the sinusoids, and that more severe disease was observed in patients who had fibrosis of both the sinusoids and the venules.

The role of the coagulation pathways in the pathophysiology of VOD is an area of controversy. Although VOD often is considered a nonthrombotic vascular disease of the liver, enough evidence exists to consider the contribution of the hemostatic system in some form. The most compelling data come from reports of effective treatment of VOD with use of thrombolytic agents and from reports of some benefit from prophylactic heparin in the prevention of VOD. Studies have shown that levels of anticoagulant proteins such as protein C, protein S, and antithrombin are decreased considerably more in patients with VOD compared with those without VOD. Whether these changes are secondary to the disease process itself or whether they lead to thrombotic occlusion of sinusoids is unclear. Changes in these proteins also have been seen after the conditioning regimen and before any clinical evidence of VOD. Levels of procoagulant proteins such as factor VIII and von Willebrand factor have been found to be higher among patients with VOD; however, these could be related to endothelial injury. Several other markers of endothelial injury, including thrombomodulin and P selectin levels, are elevated in these patients, as are levels of markers that indicate activation of the coagulation system, such as thrombin-antithrombin complexes and prothrombin fragment 1+2. Despite the substantial changes that indicate activation of the coagulation system, actual thrombi seen within the venules or sinusoids is uncommon. It is likely that the cellular debris from the sloughing of the endothelium, the subintimal thickening, and the fixed obstruction by sinusoidal and venular fibrosis play a more important role in the vascular obstruction than thrombosis. Levels of multiple cytokines, such as tumor necrosis factor α, interleukin 1, interleukin 2, and transforming growth factor β, have been shown to be elevated in patients before development of VOD and hence may be involved in its pathogenesis. Many of these cytokines are released as a response to tissue damage associated with conditioning. It is also possible that the graft-vs-host reaction contributes to the endothelial damage because the prevalence of VOD is higher in unrelated and mismatched
transplant recipients and lower in syngeneic\textsuperscript{7} and T-cell–
depleted transplant recipients.\textsuperscript{36}

The later stages of VOD are characterized by a strong
fibrotic reaction in the sinusoids; that reaction in the central
venules leads to obliteration of the venules.\textsuperscript{21} Fibrosis dem-
strated in this setting with special stains can help in
making the diagnosis. These changes can lead to signs of
chronic venous outflow obstruction. The presence of acti-
vated stellate cells has been shown in the sinusoidal region
in patients with VOD; these cells may be responsible for
the development of fibrosis in VOD.\textsuperscript{37} Elevated levels of
transforming growth factor β seen in these patients
posttransplantation also may play a role in the development
of fibrosis.

**RISK FACTORS**

Various patient characteristics pertaining to the pretrans-
plantation and transplantation phases have been implicated
in the pathogenesis of VOD (Table 1\textsuperscript{14,17,38-48}). VOD has
been seen in patients undergoing transplantation irre-
respectively of the type (allogeneic vs autologous), source of
stem cells (peripheral blood vs bone marrow), donor type
(matched vs haploidentical vs unrelated), and the type of
conditioning (conventional vs nonmyeloablative transplan-
tation). It is widely believed that the incidence of VOD is
higher in patients who undergo allogeneic stem cell trans-
plantation compared with those who undergo autologous
stem cell transplantation; however, some studies have failed
to substantiate this belief.\textsuperscript{7,17} A large study from the Euro-
pean Transplant Registry\textsuperscript{19} showed a significantly higher
incidence of VOD in allogeneic transplant recipients.

The differences observed between patients who undergo
autologous vs allogeneic transplantation may be more a
function of the differences in conditioning regimens. The
reported incidence varies between different series depend-
ing on the diagnostic criteria used. VOD tends to be more
severe in patients who undergo allogeneic transplantation,
likely a reflection of the intensity of conditioning regimens,
thus explaining the relatively higher incidence seen in stud-
ies using less sensitive diagnostic criteria. The conditioning
regimen is considered one of the important factors in the
pathogenesis of VOD; cyclophosphamide, busulfan, and/or
total body irradiation (TBI) are most commonly associated
with onset of VOD.\textsuperscript{37} In vitro and animal experiments have
 shed light on the possible mechanism of hepatic damage
due to cyclophosphamide.\textsuperscript{49} Cyclophosphamide is metabo-
lized by cytochrome P-450 in hepatocytes and is converted
into acrolein and phosphoramidate, the latter being the ther-
aputically active metabolite. Acrolein generated by hepato-
cytes damages the adjacent endothelial cells, and this pro-
cess is inhibited by glutathione.\textsuperscript{50-53} When large doses of
cyclophosphamide are administered as part of a condition-

<table>
<thead>
<tr>
<th>Table 1. <strong>Risk Factors for Veno-occlusive Disease</strong></th>
</tr>
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<tbody>
<tr>
<td>Pretransplantation factors</td>
</tr>
<tr>
<td>Preeexisting liver dysfunction (elevated transaminases, fibrosis or cirrhosis, low pseudocholinesterase level or low albumin level pretreatment)\textsuperscript{11}</td>
</tr>
<tr>
<td>Presence of hepatic metastases\textsuperscript{18}</td>
</tr>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Prior radiation treatment of the liver\textsuperscript{17}</td>
</tr>
<tr>
<td>Use of vancomycin or acyclovir in the pretransplantation period\textsuperscript{17}</td>
</tr>
<tr>
<td>Previous stem cell transplantation\textsuperscript{17}</td>
</tr>
<tr>
<td>Prior therapy with gemtuzumab ozogamicin (Mylotarg)\textsuperscript{14}</td>
</tr>
<tr>
<td>? Viral hepatitis C\textsuperscript{20,21}</td>
</tr>
<tr>
<td>? Decreased protein C\textsuperscript{42}</td>
</tr>
<tr>
<td>? Factor V Leiden mutation, prothrombin 20210 mutation\textsuperscript{43,44}</td>
</tr>
<tr>
<td>Use of norethisterone\textsuperscript{17}</td>
</tr>
<tr>
<td>Transplantation-related factors</td>
</tr>
<tr>
<td>High-dose conditioning regimens\textsuperscript{17}</td>
</tr>
<tr>
<td>Allogeneic transplantation (compared with autologous transplantation)</td>
</tr>
<tr>
<td>Busulfan for conditioning, especially when area under the curve is &gt;1500 μmol · min\textsuperscript{-1} · L\textsuperscript{-1} and combined with cyclophosphamide</td>
</tr>
<tr>
<td>Total body irradiation, especially combined with cyclophosphamide\textsuperscript{40,47}</td>
</tr>
<tr>
<td>(depends on total dose and fractionation)</td>
</tr>
<tr>
<td>Grafts from unrelated donors or related HLA mismatched transplants\textsuperscript{17}</td>
</tr>
<tr>
<td>Methotrexate as part of graft-vs-host disease prophylaxis</td>
</tr>
<tr>
<td>? Cytomegalovirus infection\textsuperscript{48}</td>
</tr>
</tbody>
</table>

**Preexisting hepatic dysfunction as evidenced by elevated transaminases, decreased albumin levels, and/or decreased pseudocholinesterase levels appears to increase patients’ risk of VOD after transplantation.**\textsuperscript{17,19,59} The presence of hepatic metastases especially in the context of solid tumors,\textsuperscript{38} prior radiation treatment of the liver,\textsuperscript{27} and pos-
sible chronic hepatitis C infection all have been reported to increase the risk of VOD. Other studies have suggested that the increased risk of VOD with hepatitis C infection occurs only in the presence of elevated transaminases. Antibiotic therapy, especially with vancomycin in the immediate pretransplantation period, has been associated with increased incidence of VOD. It is unclear whether vancomycin has any direct effect on VOD or whether it serves as a surrogate marker for recent infection. Older patients and those undergoing second transplantations are definitely at a higher risk of VOD. Some smaller reports have suggested an increased prevalence of factor V Leiden mutation and prothrombin 20210 mutation among those who develop VOD compared with those who do not. Low levels of protein C before conditioning therapy may identify patients at a higher risk of VOD. Use of methotrexate as part of graft-vs-host prophylaxis in allogeneic transplant recipients has been linked to increased risk of VOD compared with use of cyclosporine alone. It is unclear whether acute graft-vs-host disease (GVHD) can contribute to the pathogenesis of VOD. Patients receiving grafts from unrelated donors and mismatched transplants are at a higher risk for VOD, and there appears to be a decreased risk among those receiving T-cell–depleted grafts. Posttransplantation cytomegalovirus infection may increase the risk of patients developing VOD. Also, use of hormonal agents such as norethisterone has been associated with increased risk.

**CLINICAL FEATURES**

The clinical features of VOD usually appear toward the end of the first week or beginning of the second week after transplantation, and most patients who develop this complication do so within the first 3 weeks after transplantation. Some researchers have described late-onset VOD developing as late as 50 days after transplantation. Although these patients have histological features of classic VOD, it is unclear whether they actually have VOD.

The first sign in most patients is asymptomatic weight gain, believed to be due to avid retention of water and salt by the kidneys. This finding is often overlooked in these patients because they are receiving various intravenous preparations, and their weight gain is ascribed to these infusions. A few days later, isolated hyperbilirubinemia develops, which is predominantly direct bilirubin, and is gradually progressive. High levels of bilirubin and a rapid increase in the direct bilirubin level generally portend severe disease and poor outcome and are accompanied or followed by elevations in alkaline phosphatase and transaminase levels, which often vary in degree of abnormality.

Note that the laboratory finding of especially elevated alkaline phosphatase levels can be seen in other disorders such as acute GVHD or fungal infections (Table 2). The first symptom reported by patients with VOD and often the only presenting symptom is right upper quadrant pain that can be severe enough to require narcotic medications. Physical examination findings in most patients reveal an enlarged tender liver and the presence of ascites. The ascites and weight gain tend to be refractory to diuretic therapy in many patients. Evidence of renal dysfunction manifests in nearly one half of these patients, about 50% of whom require hemodialysis. A characteristic feature seen in many of these patients is thrombocytopenia refractory to platelet transfusions, although clinically severe bleeding related to thrombocytopenia is uncommon. This possibly is a result of a combination of increased consumption due to an ongoing thrombotic process in the sinusoids and increased splenic sequestration in the presence of splenomegaly related to portal hypertension. Progressive decline in hepatic function can lead to coagulation factor deficiencies and prolonged prothrombin time. As the disease progresses, some patients may develop severe encephalopathy and may even become comatose. Many of these patients develop other conditioning-related toxicities, such as diffuse alveolar hemorrhage and interstitial pneumonitis, especially in the setting of allogeneic transplantation, again highlighting the relationship of VOD to the conditioning regimen and its toxicity.

**DIAGNOSIS**

A myriad of conditions that affect the liver during the posttransplantation period can mimic the signs and symptoms of VOD (Table 2), and distinguishing VOD from these disorders remains a challenge, especially in its early stages. The gold standard for diagnosis of VOD is the histological examination of liver tissue. However, because of the danger of performing a liver biopsy in patients with thrombocytopenia often refractory to platelet transfusions, the diagnosis of VOD has been primarily based on clinical findings. The presence of hyperbilirubinemia, weight gain, and signs and symptoms of hepatic congestion form the cornerstone of the diagnosis. The diagnosis of VOD usually is made on the basis of clinical criteria put forth by the
Seattle or Baltimore groups (Table 3). In a study comparing Seattle and Baltimore criteria, a diagnosis of VOD could be confirmed on biopsy in only 42% of patients with 2 features of Seattle criteria compared with 91% of patients with all 3 features. Baltimore criteria had similar specificity but only 56% sensitivity.67

Ultrasoundography usually fails to show any parenchymal abnormality in VOD. Doppler evidence of portal hypertension, including reversal of portal flow, can help in making the diagnosis but is usually a late finding.68 Typically, ultrasoundography is more useful in excluding other disorders that can mimic VOD. Other findings on ultrasoundography include ascites, hepatomegaly, attenuated hepatic flow, and hepatic vein dilatation. Magnetic resonance imaging findings of the liver, which may complement ultrasonographic findings,69 include hepatomegaly, hepatic vein narrowing, periportal cuffing, gallbladder wall thickening, ascites, and signs of reduced portal venous flow velocity.

Histological examination of biopsy specimens is the definitive method of diagnosis. Because of the high risk of bleeding complications with percutaneous transplant biopsy in these patients, a catheter-based percutaneous transjugular approach is being used increasingly to obtain liver tissue. This procedure is associated with minimal risk of bleeding and allows the measurement of wedge hepatic venous pressures at the same time. Studies have shown that an elevated hepatic venous pressure gradient can be diagnostic in VOD, especially when it is greater than 10 mm Hg, and may even have prognostic value.70,71 One disadvantage of the transjugular approach is the small amount of tissue that can be obtained; however, with modern techniques and equipment, a representative sample adequate for making the diagnosis can be obtained. Laparoscopic approaches have been attempted to obtain more tissue. In a group of 24 patients who underwent laparoscopic biopsies during the posttransplantation period with platelet transfusion support, no complications occurred, and the procedure yielded adequate tissue in all patients.72 Advantages of the laparoscopic approach are the ability to directly visualize the liver surface and to stop bleeding from the biopsy site using cautery. However, the histological changes in the liver of patients with VOD, especially in the early stages, can be patchy and can lead to false-negative biopsy results.

Elevated plasma levels of plasminogen activator inhibitor 1 (PAI-1) are reportedly a useful marker in distinguishing VOD from other causes of posttransplantation hepatic dysfunction.73 Available evidence suggests a role for this molecule in the pathology of VOD. A decrease in the levels of PAI with use of defibrotide therapy has been seen and appears to have predictive value for patient response to this agent.74 Increased uptake of colloidal sulfur by the lungs has been suggested as a useful predictor of VOD.75 An N-

### Table 3. Diagnostic Criteria for Veno-occlusive Disease

<table>
<thead>
<tr>
<th>Seattle criteria</th>
<th>Development of at least 2 of the 3 following clinical features before day 30 after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly with right upper quadrant pain</td>
</tr>
<tr>
<td></td>
<td>Ascites and/or unexplained weight gain</td>
</tr>
<tr>
<td>Baltimore criteria</td>
<td>Development of hyperbilirubinemia with serum bilirubin &gt;2 mg/dL within 21 days after transplantation and at least 2 of the following clinical signs and symptoms</td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly, which may be painful</td>
</tr>
<tr>
<td></td>
<td>Weight gain &gt;5% from baseline</td>
</tr>
<tr>
<td></td>
<td>Ascites</td>
</tr>
<tr>
<td>Modified Seattle criteria</td>
<td>Development of at least 2 of the 3 following clinical features within 20 days after transplantation</td>
</tr>
<tr>
<td></td>
<td>Hyperbilirubinemia with serum bilirubin &gt;2 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly with right upper quadrant pain</td>
</tr>
<tr>
<td></td>
<td>Weight gain &gt;2% from baseline body weight due to fluid accumulation</td>
</tr>
</tbody>
</table>

Acute GVHD can involve the liver and result in the elevation of bilirubin and transaminase levels; when accompanied by right upper quadrant pain, GVHD is difficult to distinguish from VOD clinically. Although GVHD usually presents later (in the third week onward) in the course of transplantation compared with VOD, GVHD can present earlier or VOD can present later in the posttransplantation period. Weight gain and ascites usually are not a part of GVHD presentation, and elevation of the alkaline phosphatase level tends to be modest. Other signs such as rash and diarrhea are often present in GVHD. Confirmation of the diagnosis of GVHD by skin or other tissue biopsy can help rule out VOD; however, the 2 conditions may coexist.

Also common during the posttransplantation period are bacterial infections and septicemia, which can mimic VOD. Elevations in levels of bilirubin and often alkaline phosphatase can be seen in sepsis, although the other signs and symptoms of VOD are less common. Viral hepatitis, although unusual in this setting, should be considered in the differential diagnosis, as should cytomegalovirus infections when symptoms appear late. Various fungal infections, especially *Candida* and *Aspergillus* infections, are common in transplant recipients and can result in fungemia and hepatic infiltration with a laboratory pattern resembling that of VOD. Cyclosporine, the immunosuppressive agent most commonly used after allogeneic transplantation, various antifungal agents such as fluconazole and itraconazole, and total parenteral nutrition all can cause cholestatic hepatitis, and such causes should be ruled out. In the absence of another proven pathology, a persistent tumor, especially in the setting of documented pretransplan-
Table 4. Classification System for Severity of Veno-occlusive Disease

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Patient has no adverse effects from liver disease</td>
</tr>
<tr>
<td></td>
<td>Patient requires no treatment of veno-occlusive disease</td>
</tr>
<tr>
<td></td>
<td>Illness is self-limited</td>
</tr>
<tr>
<td>Moderate</td>
<td>Patient has an adverse effect from liver disease</td>
</tr>
<tr>
<td></td>
<td>Patient requires treatment of veno-occlusive disease (such as diuretics for fluid retention or medication to relieve pain from hepatomegaly)</td>
</tr>
<tr>
<td>Severe</td>
<td>Signs and symptoms of veno-occlusive disease do not resolve by day 100</td>
</tr>
<tr>
<td></td>
<td>Patient dies of complications directly attributable to veno-occlusive disease</td>
</tr>
</tbody>
</table>

PROGNOSIS
In most patients (50%-80%), there is a gradual resolution of the symptoms and signs over a 2- to 3-week period after onset of disease. The overall mortality from VOD varies from 20% to 50% in different series. A classification system for the severity of VOD (mild, moderate, and severe) has been proposed on the basis of the degree of hepatic dysfunction, the need for therapy, and the outcome (Table 4). Unfortunately this model gives only a retrospective assessment of the severity and is not useful for making treatment decisions.

Several prognostic factors help identify patients likely to do poorly. The degree of bilirubin elevation and the rate of bilirubin level increase seem to be 2 of the most important predictors. Bearman et al. using data from their cohort of patients, proposed a regression model based on serum bilirubin level and percentage of weight gain to identify patients at high risk for severe VOD. Since this system has low sensitivity early in the course of the disease and was validated only for regimens that include cyclophosphamide, it is not used widely. Nevertheless, it is the only model available at this time for making decisions regarding timing of intervention, and it may be useful for clinical trials evaluating preventive strategies. Patients with severe VOD develop multiple organ failure and usually die of causes other than hepatic failure (Table 5). Renal failure is common; pulmonary compromise, which often requires mechanical ventilation, is also common, as is cardiac failure, which requires inotropic support. Bacteremia develops in a considerable number of patients and can contribute to the high mortality seen in these patients. In the original series of patients reported from Seattle, the mortality rates for those with mild, moderate, and severe VOD were 9%, 23%, and 98%, respectively. Patients requiring multiple organ support have an extremely poor prognosis with near-certain death, and physicians in consultation with family members should seriously consider withdrawing life support and providing comfort care.

Late complications in those recovering from this illness are rare. In an extremely small number of patients, the hepatic damage can persist, and the severe fibrotic changes that occur can lead to long-term portal hypertension and esophageal varices.

THERAPY
Several approaches have been tried for the treatment of VOD, but none has been uniformly effective. The observation of fibrin deposition and immunohistochemical stains that show factor VIII/von Willebrand factor in the subendothelial region on liver biopsy specimens led to the evaluation of tissue-type plasminogen activator (tPA) for treatment. Multiple case reports and small series have reported resolution of symptoms in patients with established VOD after therapy with tPA. Unfortunately, in patients who usually have thrombocytopenia during this phase of illness, use of tPA has been associated with an unacceptable rate of bleeding complications. In one of the largest reports evaluating this therapy, investigators from the Seattle group reported a high rate of bleeding complications with only about a third of patients deriving any benefit; investigators did not recommend the use of tPA in these individuals. Some studies have suggested that earlier initiation of therapy may be associated with a better risk-benefit ratio. However, note that most patients with VOD improve spontaneously; hence, an earlier initiation of therapy is likely to include a large number of patients with mild VOD, and the results become difficult to generalize. Other thrombolytic agents such as urokinase have been tried but have not been studied extensively.

One of the most promising agents tried as therapy for VOD is defibrotide. Defibrotide is a novel polydeoxyribonucleotide with adenosine receptor agonist activity. Defibrotide has been shown to increase PGE2, PGI2, and thrombomodulin on the endothelial surface; decrease levels of PAI-1; and increase endogenous tPA levels. Defibrotide has no intrinsic anticoagulant properties and is not associated with any
risk of bleeding. It is well tolerated, and results from compassionate use studies have shown a 42% survival for patients with severe VOD. Results from a multi-institutional study have confirmed the benefit of this agent in the therapy for established VOD.

The importance of glutathione in protecting the sinusoidal endothelial cells from chemotherapy and possible radiation-induced damage led to the evaluation of N-acetylcysteine, a thiol antioxidant. A report of 3 patients suggested beneficial effects with N-acetylcysteine. High-dose corticosteroids have been tried with mixed results. In one study, early treatment of suspected VOD with high-dose methylprednisolone resulted in improvement in nearly two thirds of patients. However, in this study, patients were treated when they developed hyperbilirubinemia, even in the absence of other criteria for VOD. Other agents that have been used include PGE1, 89,90 glutamine, 91,92 and vitamin E, 91,92 but these were used mostly in anecdotal reports and small series.

Portosystemic shunting has been tried to reduce the elevated portal pressures seen in patients with severe VOD. Transjugular intrahepatic portosystemic shunt (TIPS) placement is an attractive method of creating a shunt in patients who are unable to undergo open procedures. Animal experiments have provided ample evidence to support the role of portosystemic shunts in the setting of hepatic venous outflow obstruction. In canine models, maintenance of portal pressure by shunt creation after hepatic venous occlusion results in preservation of hepatic energy metabolism and hepatic function. The role of the TIPS procedure in the management of advanced stages of VOD remains undefined. Isolated case reports and small case series have shown benefit in a few patients, especially those with less advanced disease. Use of the TIPS procedure has resulted in improved liver function tests and clinical signs of hepatic failure, and it can control portal hypertension in patients with severe VOD; however, it is unclear whether these improvements alter the natural course of the disease. A few patients with hepatic failure secondary to VOD have undergone liver transplantation with reports of long-term survival. This modality remains strictly experimental, however, and few institutions are capable of performing solid organ transplantsations in these extremely sick patients.

Use of charcoal hemofiltration has been reported to be effective in a small number of patients. Its use resulted in complete reversal of symptoms and signs in patients with severe VOD and bilirubin levels higher than 30 mg/dL. Our experience has been 100% mortality for patients whose bilirubin level exceeded 30 mg/dL. The mechanism behind the beneficial effect is unclear, but further studies are ongoing.

In the absence of well-defined treatments, supportive care remains the cornerstone of care for these patients. Maintaining intravascular volume and renal perfusion without causing fluid overload by optimizing sodium restriction and diuretics is extremely important. Patients should receive transfusions to keep their hematocrit levels higher than 40%; this would optimize perfusion and help maintain intravascular volume. The role of albumin or other colloids is unclear but could be considered in patients with severe hypoalbuminemia and large third space fluid accumulations. Low-dose dopamine has been used in patients with VOD and renal insufficiency because the mechanism of renal dysfunction appears to be hepatorenal in origin. Avoidance of other hepatotoxic drugs is important in these patients, and infections should be identified and treated promptly. Therapeutic paracentesis can help relieve symptoms in patients with large, tense ascites and may help improve renal function. Also, use of hemodialysis or continuous venous hemofiltration can help with fluid overload in patients with a poor response to diuretics. Peritoneovenous shunts, although useful in alleviating refractory ascites, can initiate or exacerbate disseminated intravascular coagulation. Portosystemic shunts again can help with portal hypertension and refractory ascites, but their role is unproved.

**PREVENTION**

The absence of effective therapies for VOD has spurred much interest in developing effective preventive strategies for the disease. Heparin is the best-studied agent used for prevention. Multiple studies have suggested that low-dose heparin can decrease the overall incidence of VOD, although its effect on the incidence of severe disease is unproved. In a large prospective randomized trial, administration of 100 U·kg⁻¹·d⁻¹ of unfractionated heparin started 1 week before transplantation and continued until day 30 decreased the overall incidence of VOD by nearly 10%. Use of low-molecular-weight heparin in place of unfractionated heparin can decrease the risk of bleeding episodes and has the advantage of intermittent dosing. Low-molecular-weight heparin also may accelerate platelet engraftment, but the mechanism is unclear. Ursodeoxycholic acid is administered orally and is usually well tolerated. At least 2 prospective randomized studies have shown a decreased incidence of VOD with the prophylactic use of this agent; another study showed no additional benefit when ursodeoxycholic acid was combined with heparin. Low-dose PGE, initiated before conditioning therapy and continued for 30 days after transplantation, decreased the incidence of VOD in a study involving patients with acute leukemia who received allogeneic transplants. However, other studies have been unable to re-
produce the results, and PGE1 use has been associated with considerable toxicity.107 Pentoxifylline, a xanthine derivative, has been studied in prospective trials based on initial results from small studies.85,108,109 Pentoxifylline is capable of preventing transcription of tumor necrosis factor α and stimulates endothelial production of PGI2 and PGE2. These trials showed no clinically meaningful benefits from the use of pentoxifylline, and its use was associated with adverse effects. Parenteral glutamine used prophylactically may decrease the incidence of VOD.110

CONCLUSION

Hepatic VOD is a formidable challenge both for patients undergoing stem cell transplantation and for their physicians. Hepatic VOD contributes considerably to transplantation-related morbidity and mortality. A high clinical index of suspicion is needed to correctly and consistently identify patients with VOD. Interventions using therapeutic agents such as defibrotide and N-acetylcysteine appear to hold promise, and clinical trials currently under way will provide more answers. Ongoing work, especially the development of new animal models, will help us understand the pathophysiology of VOD and enable us to develop effective interventions. Supportive care remains standard for patients developing VOD, with other interventions preferably carried out in clinical trial settings.

REFERENCES


