

Progress in the Diagnosis and Treatment of Venous Occlusive Disease/Sinusoidal Obstruction Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract: In recent years, as the technology of haploidentical transplantation has become increasingly mature, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has played an increasingly important role in the treatment of hematological diseases. However, veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) as a serious complication after allo-HSCT, has attracted much attention due to its extremely high mortality rate. This review aims to comprehensively explore the latest research progress of VOD/SOS after allo-HSCT, including epidemiological characteristics, pathogenesis, diagnostic criteria, prevention strategies and treatment regimens. First, the review summarizes the epidemiological features of VOD/SOS, pointing out that the incidence of the disease has shown a downward trend in recent years. In terms of pathogenesis, it emphasizes the core role of endothelial cell injury and the new progress in the aspects of intestinal microbiota and genetic susceptibility. Subsequently, the article reviews the updates of VOD/SOS diagnostic criteria in recent years, focusing on the quantification and clarification of the ambiguous parts in the traditional criteria, such as the optimal definition of hepatomegaly and ascites, the imaging characteristics of VOD/SOS, etc., making them more applicable in clinical practice, and further explores the new diagnostic technologies such as liver stiffness measurement and serological biomarkers. In terms of prevention, the article mainly evaluates the efficacy and safety of common prophylactic drugs for VOD/SOS. In terms of treatment, the article discusses the role of defibrotide in the treatment of VOD/SOS, and emphasizes the importance of supportive care and intensive monitoring. Finally, the review points out that although significant progress has been made in the diagnosis and treatment of VOD/SOS, further research is still needed to explore its complex pathophysiological mechanisms, to develop more specific and sensitive diagnostic criteria, and to devise more effective prevention and treatment strategies.

Keywords: Allogeneic Hematopoietic Stem Cell Transplantation; Sinusoidal Obstruction Syndrome; Diagnostic Criteria; Preventive Measure.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is a treatment method that involves collecting healthy hematopoietic stem cells and infusing them into a patient after their bone marrow has been ablated, helping to restore hematopoietic function and rebuild a normal immune system. It is still considered the only curative approach for treating a variety of hematological diseases, including aplastic anemia, various leukemias, multiple myeloma, and lymphomas. Based on the relationship between the donor and recipient, HSCT can be divided into autologous HSCT and allogeneic HSCT (allo-HSCT). In allo-HSCT, the donor is someone other than the patient themselves or an identical twin, including HLA-matched sibling donors, haploidentical related donors, and HLA-matched unrelated donors. Compared to auto-HSCT, allo-HSCT has a unique graft-versus-leukemia/tumor effect, which can specifically identify and eliminate leukemia cells, significantly reducing the risk of disease relapse. However, due to the mismatch of the immune systems between the donor and recipient, as well as the use of high-dose conditioning regimens, allo-HSCT patients are more prone to developing transplant-related complications such as graft-versus-host disease (GVHD) and veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), thereby facing a higher risk of mortality. These

factors have limited the widespread clinical application of allo-HSCT.

In recent years, with the optimization of conditioning regimens and the progress in GVHD prevention and treatment strategies, such as the use of post-transplant cyclophosphamide, the safety and efficacy of allo-HSCT have been significantly improved, making it play an increasingly important role in the treatment of hematological diseases.

VOD/SOS is a serious complication that mainly occurs in the early period after HSCT, and it is closely related to multi-organ dysfunction syndrome and has an extremely high mortality rate, which has attracted widespread attention. However, the pathogenesis of VOD/SOS has not been fully elucidated, and effective prevention and treatment methods are still lacking. More importantly, the traditional diagnostic criteria are no longer suitable for the development of modern medicine, as the subjective judgment factors not only bring confusion to the diagnosis and treatment of the disease, but also become an important factor hindering the scientific research progress in this field. The goal of this review is to provide the latest research findings on the epidemiology, pathogenesis, prevention, and treatment strategies of VOD/SOS, and to further refine the diagnostic criteria, in order to provide guidance for future research directions and clinical practice.

2. Incidence and Risk Factors

The incidence of VOD/SOS shows significant variability globally across different regions and transplant centers. Historical literature reports a wide range of overall VOD/SOS incidence, from 0% to 60%, with a median occurrence of approximately 13.7%[1]. This variability may be attributed to factors such as different diagnostic criteria, transplant center experience, patient populations, transplant types, and conditioning regimen. Studies indicate that in patients undergoing myeloablative conditioning allo-HSCT, the incidence of VOD/SOS can be as high as 10% to 15%, while it decreases to around 5% in patients receiving reduced-intensity conditioning regimens for allo-HCT[2]. Trends in the incidence rates show that a prospective study in 2005 involving 244 transplant patients reported a 20% incidence of VOD/SOS in patients with at least one VOD/SOS risk factor. Furthermore, a retrospective analysis in 2008 indicated a decrease in the cumulative incidence of VOD/SOS from 1997 to 2008 compared to 1985 to 1996 (11.5% vs. 6.5%, $P = 0.01$)[3]. Additionally, a retrospective study by EBMT in 2023 involving 2886 adult patients from 71 centers found a standardized incidence rate of VOD/SOS within 21 days post-transplant to be 1.8%, with a cumulative incidence rate within 100 days post-transplant of only 2.4%[4]. Regarding mortality, early studies suggest that the overall mortality rate of VOD/SOS may reach 50% or higher and is closely related to the severity of the disease. In severe forms of VOD/SOS, rapid liver function failure can lead to multi-organ dysfunction syndrome (MODS), involving multiple organ systems such as the lungs and kidneys, significantly worsening patient prognosis with mortality rates reaching 80%. A large retrospective study in 2018 showed that the mortality rates at 100 days and 5 years post-HSCT were 22% and 35%[5].

Risk factors for the development of VOD/SOS can be categorized into patient-related and transplantation-related factors. Patient-related risk factors include female gender, younger age, positive serology for hepatitis B or C, abnormal liver function, history of hepatotoxic drug use, low Karnofsky performance status, advanced stage of hematological disease, presence of hemophagocytic lymphohistiocytosis, elevated ferritin levels, and history of abdominal radiation. Transplantation-related risk factors encompass the type of conditioning regimen received by the recipient, CMV serostatus of the donor and recipient, HLA compatibility, use of sirolimus for GVHD prophylaxis, undergoing allogeneic transplantation, and whether it is a second transplant, among others.

In 2018, Christopher conducted a large retrospective study involving 13097 participants to analyze independent prognostic factors for VOD/SOS. Through this study, six significant risk factors were identified, including younger age, positive serology for hepatitis B, low Karnofsky performance status, use of sirolimus, disease status, and conditioning regimen. Based on these risk factors, the authors constructed a risk scoring system in a validation set and divided patients into four statistically significant groups (ABCD) based on the percentile of the risk score. The incidence rates of VOD/SOS in these groups were 1.15-1.96%, 4.34-4.43%, 8.70-9.72%, and 14.3-17.84% respectively[6]. For clinical application, the authors also provided an online VOD/SOS risk calculator website for validation and application by healthcare professionals and researchers. The online risk calculator

website is: <https://cibmtr.org/CIBMTR/Resources/Research-Tools-Calculators>.

Overall, the overall incidence and mortality rates of VOD/SOS are showing a decreasing trend, and historical literature on incidence rates may not reflect the current situation in the medical context. This trend may be attributed to advancements in diagnostic criteria, optimization of conditioning regimens, development of preventive and therapeutic drugs, improvement in donor selection and transplant procedures, as well as the progress in supportive care, intensive monitoring, and nursing treatment. Currently, there is no widely accepted prognostic model, with Professor Christopher's model being the most well-known, but it also has significant limitations, such as not including specific diseases and niche conditioning regimens, limited comparison of individual variables, lack of comparison on efficacy, survival, and severity, and requires multiple repetitions, especially prospective studies, for validation.

3. Pathogenesis

VOD/SOS is considered a complex pathological process involving multiple factors, including endothelial injury, coagulation activation, and inflammatory response. Studies have shown that sustained exposure to various toxic factors, such as conditioning regimens, inflammatory cytokines, endogenous microbiota, and calcineurin inhibitors, can lead to excessive activation of sinusoidal endothelial cells. These activated endothelial cells release heparinase, which degrades the extracellular matrix proteins and disrupts the cytoskeletal structure, impairing the tight junctions between cells and increasing the intercellular gaps in the sinusoidal barrier. Subsequently, cellular debris such as red blood cells and leukocytes infiltrate the Disse space, leading to endothelial cell detachment, downstream thrombosis of the central veins, and sinusoidal obstruction, which may ultimately progress to liver failure, multi-organ dysfunction syndrome, and even death[7,8]. The overactivation of endothelial cells can also activate the coagulation pathway, leading to upregulation of coagulation factors and an imbalance in the coagulation-fibrinolysis system, resulting in microthrombotic obstruction of the sinusoids. Meanwhile, endothelial injury and microthrombosis trigger an inflammatory response, releasing proinflammatory cytokines and chemokines, which further exacerbate endothelial injury and sinusoidal obstruction.

The glutathione (GSH) system can detoxify some drug metabolites, such as cyclophosphamide metabolites, and previous liver disease, busulfan, and total body irradiation can all affect the GSH system, leading to the accumulation of cyclophosphamide metabolites, which can damage sinusoidal endothelial cells and hepatocytes[9]. The acinar zone 3 is more susceptible to endothelial injury due to the lack of GSH. This also explains the higher incidence in pediatric patients due to the immaturity of the GSH system, and provides new insights for the prevention and treatment of VOD/SOS.

Furthermore, Jonathan et al. analyzed 8,767 fecal samples from HSCT patients and found that the higher the diversity of the gut microbiome, the lower the mortality risk (cohort 1: HR 0.71, 95%CI 0.55-0.92; cohort 2: HR 0.49, 95%CI 0.27-0.90)[10]. Laurie et al. confirmed through rat models and in vitro experiments that cyclophosphamide can induce sinusoidal obstruction syndrome, and the potential mechanism may involve cyclophosphamide-induced F-actin depolymerization and increased matrix metalloproteinase

activity in sinusoidal endothelial cells[8]. A 2021 meta-analysis indicated that genes such as GSTA1, MTHFR, CPS1, CTH, CYP2B6, GSTM1, GSTP1, HFE, and HPSE may be associated with the development of VOD/SOS[11].

In summary, the pathogenesis of VOD/SOS has not been fully elucidated, but endothelial injury in the sinusoidal space is considered the dominant role, with the activation of coagulation mechanisms, the occurrence of inflammatory responses, and the detoxification mechanism of the glutathione system also being important influencing factors. As cell biology and molecular biology research continues to deepen, some new potential mechanisms are being explored and discovered, such as the role of the gut microbiome, the process of F-actin depolymerization, and related genetic markers, providing new perspectives for understanding VOD/SOS.

4. Diagnostic Criteria

4.1. Traditional Diagnostic Criteria

For a long time, the diagnosis of VOD/SOS has mainly relied on the Baltimore criteria proposed by Jones et al. in 1987 and the modified Seattle criteria proposed by McDonald et al. in 1993. The Baltimore criteria define VOD/SOS as the occurrence of two or more of the following symptoms within 21 days after transplantation: total bilirubin level exceeding 2 mg/dL, painful hepatomegaly, and weight gain exceeding 5% of baseline. The modified Seattle criteria define VOD/SOS as the occurrence of at least two of the following symptoms within 20 days after transplantation: acute hepatomegaly or right upper quadrant pain, weight gain exceeding 2% of baseline, total bilirubin level exceeding 2 mg/dL (34.2 $\mu\text{mol/L}$), and ascites. The main changes in the modified Seattle criteria include no longer requiring an increase in total serum bilirubin as a necessary diagnostic condition, reducing the percentage of weight gain, and adding ascites as a diagnostic criterion. A retrospective study of 845 HSCT patients reported that according to the Seattle criteria, 117 patients were diagnosed with VOD/SOS, while according to the Baltimore criteria, 73 patients were diagnosed, with cumulative incidences of 13.8% and 8.8%, respectively[3].

The Seattle criteria and Baltimore criteria have certain limitations. First, the time window restriction, as both limit the occurrence of VOD/SOS to within 21 days after HSCT, which may lead to the neglect of late-onset VOD/SOS. Secondly, the lack of sensitivity and specificity, as the traditional criteria mainly rely on clinical symptoms and biochemical indicators, without comprehensive consideration of imaging examination results, and these two diagnostic criteria are also inconsistent, leading to confusing diagnostic results. Compared to the Baltimore criteria, the use of the Seattle criteria may result in a higher incidence of VOD/SOS diagnosis.

4.2. EBMT Criteria

To address the limitations of the existing diagnostic criteria, The European Society for Blood and Marrow Transplantation (EBMT) introduced a set of updated diagnostic guidelines in 2018. In the adult diagnostic criteria, EBMT adjusted the modified Seattle criteria, setting the standard for weight gain at exceeding 5% of baseline, and defining this as classic VOD/SOS. Additionally, EBMT introduced the concept of late-onset VOD/SOS, defining it as cases occurring more than 21 days after HSCT, including cases with classic VOD/SOS

features, histologically confirmed VOD/SOS, or cases meeting at least two of the four classic VOD/SOS criteria based on hemodynamic or imaging evidence[12].

Given the differences in clinical manifestations of VOD/SOS between pediatric and adult patients, such as a higher proportion of late-onset and non-jaundiced patients, as well as differences in risk factors, EBMT established independent diagnostic criteria specifically for children. These criteria require patients to meet at least two of the following conditions: consumption coagulopathy unresponsive to platelet transfusion, unexplained weight gain or weight gain exceeding 5% of baseline for three consecutive days unresponsive to diuretics, total bilirubin level higher than baseline or $\geq 34 \mu\text{mol/L}$ within 72 hours, and hepatomegaly or ascites confirmed by imaging examination[12].

EBMT also developed a grading system for the severity of VOD/SOS, which classifies VOD/SOS patients into mild, moderate, severe, and very severe categories based on key indicators such as the time from onset to diagnosis, bilirubin level and its trend, transaminase levels, serum creatinine, and the degree of weight gain.

Overall, the EBMT criteria have made significant progress in identifying late-onset cases and pediatric patients, particularly by adjusting the diagnostic window, grading the severity of the disease, and emphasizing the importance of imaging and histological examinations in the diagnostic process. The disease severity grading system is valuable for early diagnosis of VOD/SOS, providing guidance for treatment, and conducting comprehensive risk assessment.

4.3. Quantification and Supplementation of Existing Standards

In the three existing diagnostic criteria, some content has a strong subjective nature, and specific explanations are not provided in the standards, which may cause difficulties in clinical practice. Therefore, we have summarized the understanding of the ambiguous content in the previous standards of different centers, further clarifying and quantifying key indicators such as hepatomegaly, ascites, and thrombocytopenia, and supplementing the specific manifestations of imaging and biopsy examinations, in order to improve the accuracy and consistency of VOD/SOS diagnosis.

The best definition of hepatomegaly is an absolute increase of at least 1 cm in the liver length along the midclavicular line. If there is no baseline measurement available for reference, hepatomegaly can be defined as exceeding the normal liver size of the same age by more than 2 standard deviations[13]. Ascites can be classified as mild (only a small amount of fluid in the liver, spleen, or pelvis), moderate (fluid volume less than 1 cm), or severe (fluid accumulation in all three regions, with at least two regions having a fluid volume exceeding 1 cm)[14].

EBMT defines platelet transfusion refractoriness in children as the need for daily platelet transfusions appropriate for their body weight after excluding other causes. Furthermore, the international expert consensus suggests that the use of the corrected count increment (CCI) can more accurately assess the efficacy of platelet transfusion in children with VOD/SOS. Platelet transfusion refractoriness is defined as a CCI less than 5,000 to 7,500 (approximately 3×10^{11} platelets per single-donor platelet unit) after two consecutive transfusions of the same type of platelets[12].

Liver biopsy is the gold standard for the diagnosis of VOD/SOS, with pathological features including sinusoidal dilatation, hepatocyte atrophy and necrosis, collagen fiber deposition in the sinusoids and terminal hepatic veins, and complete obstruction of the central veins[15,16]. Measurement of the hepatic venous pressure gradient (HVPG) by transjugular liver biopsy has good accuracy and specificity in predicting VOD/SOS, with HVPG >10 mmHg.

The ultrasonographic features of VOD/SOS include decreased or reversed portal venous flow, increased liver volume, narrowed hepatic veins, dilated and slow portal veins, ascites, and rough gallbladder wall[13,17]. Unenhanced CT scans usually reveal hepatomegaly, ascites, and heterogeneous liver density. Contrast-enhanced CT scans may show thickened and tortuous hepatic arteries, mildly heterogeneous liver parenchymal enhancement, "map-like" changes, obscured hepatic veins and inferior vena cava, and the "halo sign" or "target sign"[18]. MRI findings are similar to CT in unenhanced scans, while contrast-enhanced scans may show lack of parenchymal enhancement in the arterial phase, patchy enhancement in the portal venous phase, and delayed narrowing or obstruction of the right hepatic vein[19].

Overall, further quantification and clarification of the diagnostic criteria can help reduce missed diagnoses and misdiagnoses in clinical practice. Color Doppler ultrasound is considered the preferred imaging modality due to its portability, safety, cost-effectiveness, and good performance in observing portal venous flow. Gallbladder wall thickening and ascites accumulation are considered independent predictors of VOD/SOS progression, and decreased or reversed portal venous flow is usually seen as a late-stage sign of the disease. MRI and CT have unique value in differentiating GVHD. Although invasive examinations have high specificity, their clinical application is limited. We look forward to the emergence of a practical and sensitive examination method.

4.4. New Techniques in VOD/SOS Diagnosis

4.4.1. Liver Stiffness Measurement (LSM)

The emerging LSM technology, particularly liver stiffness monitoring using transient elastography, has become a key research area for the diagnosis of VOD/SOS. In a retrospective study by Inoue in 2023, 14 out of 86 adult patients (13%) developed VOD/SOS, and their LSM values after HSCT all exceeded 17.4 kPa, with a sensitivity and specificity of 100% and 90.3%, respectively[20]. In a retrospective study by Ozkan in 2022 of 49 HSCT patients, LSM values were generally higher in VOD/SOS patients, but did not increase significantly in patients with bilirubin levels below 2 mg/dL[21]. Further studies have shown that the increase in LSM can be detected 1 to 15 days before the clinical diagnosis of VOD/SOS and gradually decreases with VOD/SOS treatment, further confirming the effectiveness of LSM in monitoring treatment response. A prospective Italian study validated the above conclusions, showing that the diagnostic performance of LSM increase for VOD/SOS was extremely high, with an area under the receiver operating characteristic curve of 0.997 (sensitivity 75%, specificity 98.7%), and LSM values did not increase significantly in patients with other liver-related complications other than VOD/SOS[22].

As a potential alternative to HVPG, LSM has shown promise as a non-invasive imaging technique in multiple retrospective studies and some single-center prospective

studies. The characteristic changes in LSM appear earlier than the onset of clinical symptoms and laboratory indicators, and are significantly correlated with the progress of treatment. Furthermore, LSM can also help differentiate other liver-related complications. Therefore, LSM is expected to be widely used in the early diagnosis, differential diagnosis, and efficacy evaluation of VOD/SOS. Of course, more prospective studies are needed to validate these findings.

4.4.2. Serological Biomarkers

In VOD/SOS research, the expression levels of certain protein and metabolite markers are elevated in patient serum, providing new clues for early diagnosis and treatment. Specifically, markers such as KL-6, surfactant protein D (SP-D), surfactant protein A (SP-A), lactate dehydrogenase (LDH), and bilirubin are associated with the occurrence and severity of VOD/SOS. Current research on VOD/SOS serological markers mainly focuses on sinusoidal endothelial injury and coagulation dysfunction. Key serological markers include endothelial injury markers such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), angiopoietin-2 (ANG-2), and ST2, as well as coagulation function markers such as plasminogen activator inhibitor-1 (PAI-1) and inflammatory-related cytokines such as tumor necrosis factor- α (TNF- α) and interleukins (IL series)[23–27].

Overall, although these markers have shown potential in the diagnosis of VOD/SOS, there is currently no widely recognized and clinically applied specific biomarker. PAI-1 and ANG-2 are the most promising serological predictive markers, suggesting the possibility of a sensitive and effective non-invasive detection method.

5. Preventive Measures

VOD/SOS is a major cause of early mortality after HSCT, with a high mortality rate but limited treatment options. Therefore, prevention of VOD/SOS is of utmost importance. The main preventive measures for post-HSCT VOD/SOS include pharmacological prophylaxis, modification of risk factors, and close monitoring of patient status. The key pharmacological agents currently used for VOD/SOS prophylaxis include heparin, prostaglandin E1 (PGE1), Defibrotide (DF), ursodeoxycholic acid (UDCA), and low-dose recombinant tissue plasminogen activator.

UDCA is a non-toxic hydrophilic bile acid believed to have a protective effect on the liver. It may reduce VOD/SOS through mechanisms such as neutralizing toxic bile acid molecules, alleviating oxidative stress, and stabilizing hepatocyte membranes, thereby mitigating sinusoidal endothelial cell injury. A 2000 prospective study of 132 patients showed UDCA significantly reduced the incidence of VOD/SOS (18.5% vs. 3.0%, $p=0.0043$)[28]. However, a 2002 randomized trial of 242 allogeneic HSCT patients found no statistically significant difference in VOD/SOS incidence between the UDCA and control groups (2.4% vs. 4.2%, $p=0.45$)[29], leading to further debate on the efficacy of UDCA for VOD/SOS prophylaxis.

DF is a mixture of oligodeoxyribonucleotides extracted from porcine mucosa, with potent anti-coagulant and anti-inflammatory properties. DF can increase prostaglandin and plasminogen activator levels, and attenuate endothelial cell activation, thereby protecting the sinusoidal vasculature. Two large prospective studies reached different conclusions on its prophylactic efficacy. A 2012 pediatric study showed a

VOD/SOS incidence of 12% in the DF group versus 20% in controls ($p=0.0488$) [30]. However, a 2022 study in adults and children found no statistically significant difference in VOD/SOS-free survival between the DF prophylaxis and best supportive care groups ($p=0.85$), leading to early termination due to futility [31]. Based on this, the European Medicines Agency (EMA) has recommended against using Defibrotide for VOD/SOS prophylaxis. Some retrospective studies have suggested a potential role for DF, especially in high-risk pediatric patients [32]. Bleeding events, particularly pulmonary hemorrhage, are the most prominent adverse reactions associated with DF use for both prophylaxis and treatment of VOD/SOS.

The proposed mechanism of low-molecular-weight heparin in preventing VOD/SOS is its inhibition of the coagulation cascade and reduction of microthrombosis. A Chinese study recommended prophylactic use of low-dose heparin at 100 IU/kg/day by continuous intravenous infusion for 7 days pre-transplant to 14 days post-transplant [33]. A study of 2,572 HSCT recipients found that prophylactic use of UDCA and intravenous heparin or PGE1 reduced the incidence of post-HSCT VOD/SOS to 3.4%. However, a meta-analysis of 2,782 patients showed no benefit from using unfractionated or low-molecular-weight heparin for VOD/SOS prophylaxis, and instead found an increased risk of bleeding (RR 0.90; 95% CI 0.62-1.29) [34]. Increased bleeding risk, thrombocytopenia, and impaired liver and kidney function are considered the main adverse effects of heparin.

PGE1 has been considered to have potential for VOD/SOS prophylaxis due to its vasodilatory and anti-inflammatory properties, but the current evidence is still insufficient. Its adverse effects include skin erythema and desquamation, severe limb pain, fluid retention, edema, and hypertension [35].

Overall, the efficacy of current pharmacological agents for VOD/SOS prophylaxis remains controversial, mainly due to inconsistent study results and safety concerns. Only UDCA has been included in the British Committee for Standards in Hematology guidelines, but this recommendation has not gained widespread international acceptance. The EMA does not recommend using Defibrotide for VOD/SOS prophylaxis. These situations highlight the urgent need to discover and develop truly effective VOD/SOS preventive medications.

6. Treatment

The treatment of VOD/SOS includes pharmacological therapy, intensive care, and supportive treatment, involving fluid management, pain control, nutritional support, and management of potential complications.

DF exhibits its antithrombotic and anti-inflammatory effects by improving microcirculation and alleviating endothelial damage. Results from a prospective multicenter study of 104 VOD/SOS patients treated with DF showed that 73% of severe cases had resolution by day 100, with a Kaplan-Meier estimated survival rate of 73% [36]. Another analysis of 414 patients revealed that 73% experienced resolution of VOD/SOS after DF treatment, with a resolution rate of 59.5% in adults and 92% in children with severe cases [37]. Common side effects of defibrotide include an increased tendency for bleeding.

Overall, DF has demonstrated benefits for VOD/SOS patients in multiple studies, including symptom improvement, shortened treatment duration, and increased survival rates. It is currently the only drug considered effective in treating

VOD/SOS. When using defibrotide for VOD/SOS treatment, close monitoring of patients' coagulation parameters and bleeding symptoms is necessary. Early diagnosis and treatment are crucial, and for high-risk patients, systematic screening and assessment are vital for prompt diagnosis and treatment initiation.

7. Summary

VOD/SOS is a severe complication following HSCT with a high mortality rate. The pathogenesis of VOD/SOS involves complex pathological processes such as endothelial injury, coagulation activation, and inflammatory responses. Mechanisms including intestinal microbiota and genetic susceptibility are still under exploration. Currently, there is no internationally recognized VOD/SOS risk prognostic model, with Professor Christopher's risk model being the most well-known. Apart from UDCA recommended by the British Committee for Standards in Hematology, there is a lack of widely accepted drugs for VOD/SOS prevention. DF is the only drug proven effective in treating VOD/SOS, approved in the US and Europe for patients with pulmonary dysfunction or severe VOD/SOS. Despite multiple revisions, VOD/SOS diagnostic criteria are mainly based on clinical manifestations, subjective, and some criteria need further quantification. Due to the lack of specific clinical features and sensitive biomarkers, distinguishing VOD/SOS from other transplant complications is challenging. Doppler ultrasound is considered the most reliable imaging method for supporting VOD/SOS diagnosis, while invasive diagnostic methods like biopsy or hepatic venous pressure gradient measurement are not widely used in clinical practice. The development of LSM and serum markers offers the potential for establishing safe, sensitive non-invasive diagnostic methods. Future research needs to further explore the specific pathogenic pathways of VOD/SOS, validate potential therapeutic targets, and provide new strategies for the prevention and treatment of this disease.

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