DukeMedicine
Division of Cellular Therapy

ADULT AND PEDIATRIC BLOOD AND MARROW TRANSPLANT PROGRAM

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DOCUMENT TITLE:
Veno-Occlusive Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS) Prophylaxis, Diagnosis and Treatment

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APBMT-COMM-015
VENO-OCCLUSIVE DISEASE (VOD)/SINUSOIDAL OBSTRUCTION SYNDROME (SOS) PROPHYLAXIS, DIAGNOSIS, AND TREATMENT

1 PURPOSE

1.1 To provide a consistent approach to the prevention of hepatic veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) in autologous and allogeneic hematopoietic stem cell transplant recipients. Guidelines for diagnosis and treatment of VOD/SOS are also reviewed.

1.2 To provide a consistent approach to the treatment of veno-occlusive disease/sinusoidal obstruction syndrome in autologous and allogeneic transplant recipients

2 INTRODUCTION

2.1 Several Factors have been associated with an increased risk of developing VOD/SOS:

- 2.1.1 Transplant Related:
  - 2.1.1.1 Unrelated donor
  - 2.1.1.2 HLA-Mismatched donor
  - 2.1.1.3 Prior stem cell transplantation
  - 2.1.1.4 Non T-cell depleted Transplant
  - 2.1.1.5 Radiation (high-dose TBI based regimens)
  - 2.1.1.6 Myeloablative-conditioning regimens
- 2.1.2 Patient Characteristics and Disease Related
  - 2.1.2.1 Older age and younger age including infants
  - 2.1.2.2 Karnofsky score less (<) than 90%
  - 2.1.2.3 Thalassemia
  - 2.1.2.4 Genetic Factors
  - 2.1.2.5 Utilization of Progestin Therapy
  - 2.1.2.6 Elevated ferritin
  - 2.1.2.7 Presence of Iron Overload
  - 2.1.2.8 Advanced disease (beyond second CR or relapse/refractory)
- 2.1.3 Hepatic Related
  - 2.1.3.1 Pre-existing Liver Disease
  - 2.1.3.2 Prior inotuzumab or gemtuzumab therapy
  - 2.1.3.3 Exposure to Abdominal or Hepatic Radiation

2.1.3.4 Transaminases greater than 2.5 ULN

2.1.3.5 Bilirubin greater than 1.5 ULN

2.1.3.6 Exposure to Hepatotoxic drugs

2.1.3.7 Presence of Iron overload

3 SCOPE AND RESPONSIBILITES

3.1 The Adult and Pediatric Blood and Marrow Transplant (APBMT) medical team will provide medical management of the patient.

3.2 The nursing staff will provide supportive care and administer any treatment ordered by the medical team.

4 DEFINITIONS/ACRONYMS

4.1	ANC	Absolute Neutrophil Count
4.2	aPTT	Activated Partial Thromboplastin Time
4.3	APBMT	Adult and Pediatric Blood and Marrow Transplant
4.4	ATIII	Antithrombin III
4.5	BID	Twice a day
4.6	FFP	Fresh Frozen Plasma
4.7	HSCT	Hematopoietic Stem Cell Transplantation
4.8	SOS	Sinusoidal Obstruction Syndrome
4.9	TID	Three times a day
4.10	VOD	Veno-occlusive Disease

5 MATERIALS

5.1 NA

6 EQUIPMENT

6.1 NA

7 SAFETY

7.1 NA

8 PROCEDURE

8.1 Population specific considerations:

8.1.1 Adult Program:

8.1.1.1 Prophylaxis with ursodiol as follows:

8.1.1.1.1 Ursodiol 300 mg PO twice a day (BID) or 300 mg PO three times a day (TID) if weight

is greater than (>) 90 kg beginning with the conditioning regimen or up to 3 weeks prior to starting the conditioning regimen.

8.1.1.1.2 Continuing through day +30 for autologous patients

8.1.1.1.3 Continuing through day +90 for allogeneic patients

8.1.1.1.4 Patients receiving melphalan alone will NOT receive VOD/SOS prophylaxis unless otherwise directed.

8.1.1.2 Alternative regimen:

8.1.1.2.1 Heparin 100 units/kg/day will be administered as a continuous infusion beginning prior to initiation of the preparative regimen and continuing until 28 days or the time of engraftment defined as absolute neutrophil count (ΛNC) greater than or equal to 500 cells/mm3; monitoring of the activated partial thromboplastin time (aPTT) is not required; patients should be monitored for signs and symptoms of bleeding.

8.1.2 Pediatric Program

8.1.2.1 Prophylaxis with ursodiol as follows:

8.1.2.1.1 Ursodiol 10 mg/kg by mouth TID (maximum dose: 300 mg by mouth 3 times a day).

8.1.3 Alternative regimen:

8.1.3.1 Heparin 100 units/kg/day will be administered as a continuous infusion beginning prior to initiation of the preparative regimen and continuing until 28 days or the time of engraftment defined as ANC greater than or equal to 500 cells/mm3; monitoring of the aPTT is not required; patients should be monitored for signs and symptoms of bleeding.

NOTE: Heparin therapy in infants weighing less than (<) 10kg may be reduced to 10 units/kg/hour.

8.2 Additional Considerations:

8.2.1 For patients with multiple risk factors:

8.2.2 Consider avoiding azoles during preparative chemotherapy and until Day +30 of transplant.

8.2.3 For patients with a high risk for the development of VOD/SOS

8.2.4 Consider baseline imaging with ultrasound, when feasible.

8.2.5 Consider prophylaxis with Defibrotide (Refer to Defibrotide Guidelines for Use in Adults and Pediatrics).

8.3 Signs or symptoms of VOD/SOS include the following below however diagnosis is generally based on diagnostic criteria (see "Diagnosis" in subsequent sections below):

8.3.1 Weight gain (greater than 5% of initial body weight)

8.3.2 Right upper quadrant pain

8.3.3 Hyperbilirubinemia

8.3.4 Ascites

8.3.5 Coagulopathy (low antithrombin III (ATIII), low factor VII)

8.3.6 Reversal of flow on hepatic doppler ultrasound

8.3.7 Renal insufficiency

8.4 Diagnosis

8.4.1 Diagnosis generally utilizes published diagnostic criteria. One such criteria is seen in Figure 1 below.

Figure 1. New EBMT Diagnostic Criteria for Adults and Pediatrics

New EBMT diagnostic criteria for adults and pediatrics

Adults

Classical SOS/VOD In the first 21 days after HSCT	Late onset SOS/VOD Greater than 21 days after HSCT
Bilirubin greater than or equal to 2 mg/dL and two of the following criteria must be present: • Painful hepatomegaly • Weight gain greater than 5% • Ascites	Classical VOD/SOS beyond day 21 OR Histologically proven SOS/VOD OR Two or more of the following criteria must be present: • Bilirubin greater than or equal to 2 mg/dL • Painful hepatomegaly • Weight gain greater than 5% • Ascites AND hemodynamically and/or ultrasound evidence of SOS/VOD

Pediatrics

- No limitation for time of onset of SOS/VOD

The presence of two or more of the following[a]

- Unexplained consumptive and transfusion-refractory thrmobocytopenia[b]
- Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain greater than 5% above baseline value
- [c]Hepatomegaly (best if confirmed by imaging) above baseline value
- [c]Ascites (best if confirmed by imaging) above baseline value
- Rising bilirubin from a baseline value on 3 consecutive days or bilirubin greater than or equal to 2 mg/dL within 72 h

[a]With the exclusion of other potential differential diagnoses.

[b] Greater than or equal to 1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.

[c] Suggested: imaging (ultrasonography, computed tomography or magnetic resonance imaging) immediately before HCT to determine baseline value for both hepatomegaly and ascites.

8.5 Severity Grading

8.5.1

Severity Grading criteria has been established to help guide therapy decisions. One such criteria is the EBMT Criteria for severity grading of suspected SOS/VOD. Criteria exists for Adults and for Pediatrics as seen in Figure 2 and Figure 3 respectively below.

Figure 2. EBMT Criteria for severity grading of suspected SOS/VOD in Adults

Parameter	Mild[a]	Moderate[a]	Severe	Very severe – MOD/MOF[b]
Time since first clinical symptoms of SOS/VOD[c]	>7 days	5-7 days	≤4 days	Any time
Bilirubin (mg/dL)	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin kinetics			Doubling within 48h	
Transaminases	≤2 x normal	>2 and ≤5 x normal	>5 and ≤8 x normal	>8 x normal
Weight increase	<5%	≥5% and <10%	≥5% and <10%	≥10%
Renal function	<1.2 x baseline at transplant	≥1.2 and < 1.5 x baseline at transplant	≥1.5 and <2 x baseline at transplant	≥2 x baseline at transplant or other signs of MOD/MOF

[a]In the case of presence of two or more risk factors for SOS/VOD, patients should be in the upper grade.

[b]Patients with multi-organ dysfunction must be classified as severe

Figure 3. Modified EBMT Criteria for severity Grading of Suspected SOS/VOD in Pediatrics

Parameter	Mild	Moderate	Severe	Very Severe MOD/MOF
Bilirubin (mg/dL)	<2	2-3	>3	Persistent rise
Coagulopathy (INR)	<1.5	1.5-1.9	>2	Need for replacement of coagulation factors
Ascites	None	Mild	Moderate	Refractory to medical management
Weight gain	2.5%	5-10% despite diuretic use	>10%	Persistent rise
KDIGO	Serum creatinine 1.5-1.9 times baseline OR ≥0.3 mg/dL (≥26.5 mmol/L) increase OR Urine output <0.5 mL/kg/h for 6-12 hours	Serum creatinine 2-2.9 times baseline OR Urine output <0.5 mL/kg/h for ≥12 hours	Serum creatinine 3 times baseline OR Increase in serum creatinine to ≥4 mg/dL (≥353.6 mmol/L) OR Initiation of renal replacement therapy OR In patients <18 years, decrease in eGFR to <35 mL/min/1.73m² OR Urine output <0.3 mL/kg/h for ≥24 hours or anuria for ≥12 hours	Persistent need for renal replacement therapy
Encephalopathy			CAPD >9	
Ultrasound	Hepatopetal flow	Parvus tardus waveform	Hepatofugal flow	-
Persistent RT	<3 days	3-7 days		>7 days
Pulmonary Function	<2L	<2L	Non-invasive ventilation/invasive mechanical ventilation	Persistent need for invasive mechanical ventilation

KDIGO=Kidney Disease: Improving Global Outcomes score. CAPD=Cornell Assessment of Pediatric Delirium. RT=refractory thrombocytopenia.

8.6 Treatment Options

8.6.1 Consider Defibrotide

- See related Duke University Hospital guidelines: Defibrotide Guidelines for Use in Adults and Pediatrics

8.6.2 Consider Symptom Management

- Maintain fluid balance/Fluid Restriction/Diuresis

- Hepatorenal Management
- Diuretics such as furosemide or spironolactone
- Initiate additional supportive measures as clinically indicated (e.g. Fresh Frozen Plasma (FFP), Factor VII concentrate, ATIII concentrate, draining of ascites, ursodiol).
- Plasmapheresis
- Intrahepatic shunting
- Draining of ascites if they cause respiratory compromise
- Factor VII replacement therapy
- Ursodiol

8.7 Reportable conditions:

8.7.1 Intolerance or allergy to prophylactic regimen; active bleeding.

8.7.2 Veno-occlusive Disease/Sinusoidal Obstruction Syndrome

9 RELATED DOCUMENTS

9.1 DUH Guideline: Defibrotide Guidelines for Use in Adults and Pediatrics.

10 REFERENCES

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11 REVISION HISTORY

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07	S. McCollum	Introduction section – updated to broaden Risk Factors Section 8- Significant formatting throughout to group adult and pediatric information accordingly. Section 8- updated to include EBMT diagnostic Criteria Section 8 – updated to include EBMT severity grading criteria Section 8- regrouping of treatment options into categories Section 10- Additional references were added

Signature Manifest

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