Bone Marrow Transplant Programme Guideline

***Clinical Guidelines** are "policy and/or guideline" documents.*
They do not require a competency, but each document must be registered with the Trust.

Title: **Guideline for the Diagnosis and Management of Veno-Occlusive Disease**

Index Code: Guideline PRB44

Version: 8.0

Area of Application: Clinical Unit – Fletcher Ward, Toghill Ward, Haematology Day Case & Outpatients

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Amendments to Version :

Version	Amendment	Released	Implemented	Archived
6.1	**Early review and update against JACIE 7th edition.** **Section 6.1:** risk factors updated **Section 6.2:** Instruction added for use of ursodexycholic acid. **Section 6.5.3:** Second line therapy rewritten. **Section 9:** References updated.	05-FEB-2019	05-FEB-2019	06-April-2021
7.0	**Review against JACIE 7th edition** **Updated the use of Defibrotide policy – [P200804P]**	06-Apr-2021	06-Apr-2021	03-08-2021
7.1	**Note added to section 6.1: avoid the use of Paracetamol when treating patient with Busulfan**	03-08-2021	03-08-2021	07-Sept-2021
7.2	**Updated SOP format as per SOP A01**	07-Sept-2021	07-Sept-2021	09/11/2023
8.0	**Full review completed following new commissioning policy** **Severity grading criteria added and amendment to Urso to day +100**	09/11/2023	09/11/2023	

Contents

1. Principles and Purpose / Objective:

This document describes the diagnostic criteria and management plan for VOD of the liver.

Veno-occlusive disease of the liver is characterised by endothelial injury and non thrombotic obstruction of small intra-hepatic venules leading to liver damage. Hepatic VOD is recognised as one of the most common and important regimen-related toxicities experienced after allogeneic and autologous stem cell transplantation. VOD is a clinical syndrome characterised by painful hepatomegaly, jaundice, ascites, fluid retention and weight gain. The onset is usually before day +35 after stem cell infusion and other causes of these symptoms are absent.

VOD develops in approx. 14% (5-60%) of patients after SCT and ranges in severity from mild, reversible disease to a severe syndrome associated with multi-organ failure (MOF) and death, with established severe VOD shown to have a mortality rate approaching 100% by day + 100 post SCT.

2. Related Documentation:

- BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation.
- NHS England B04/P/c Clinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease following stem cell transplant. March 2021 . ([P200804P] stored in policy's on the NUH intranet)

3. Terminology, Abbreviations and Definitions:

See Glossary in current Bone Marrow Transplant Programme Operational Policy and Quality Manual.

VOD - veno-occlusive disease

TLCO - transfer factor for carbon monoxide

MOF – multi-organ failure

SCT – stem cell transplant

Blueteq form - individual funding request for Specialised Commissioning Prescribing

4. Personnel and Training Requirement:

- Nursing and Clinical staff in Clinical Haematology.

5. Equipment:

Not applicable

6. Procedure / Method:

6.1. Risk Factors

The following factors have been observed to be associated with an increased risk of developing VOD:

- Conditioning chemotherapy: Busulfan has been associated with a higher incidence of VOD
- Prior abdominal radiation
- Abnormal TLCO (>70% of predicted)
- Pre-existing liver disease: including tumour involvement, viral hepatitis, fatty liver degeneration, alcohol abuse and chemotherapy-induced liver damage. **A raised AST or ALT level or Bilirubin >26 umol/L pre-SCT should be considered as a risk factor**.

- Previous or current Hepatitis B and C infection
- CMV seropositivity: it has been shown in some studies to be correlated with a high incidence of VOD, although it remains controversial.
- Persistent fever or infection prior to SCT: especially if treated with Vancomycin, Amphotericin and/or Aciclovir.
- Ongoing treatment with azoles for fungal infections.
- Allogeneic stem cell transplantation: especially from an unrelated donor or a haplo-identical donor.
- Previous SCT or previous prolonged and/or high dose chemotherapy
- Previous treatment with gemtuzumab or inotuzumab
- Norethisterone for prevention of menstrual bleeding.
- Iron overload.

NOTE: Patients receiving a dose of Busulfan or Treosulfan should not be given Paracetamol 72 hours prior to the first dose, during treatment or 72 hours post Bulsulfan/Treosulfan treatment.

6.2. Prophylaxis

Defibrotide is not funded for prophylactic use and should not be used

Prophylaxis with ursodeoxycholic acid (300mg BD) should be started from the start of conditioning for all high risk patients as identified in section 6.1, above, and for all patients on the following conditioning regimens.

Flu-Bu-ATG

FLAMSA-Bu

Flu-Treo-ATG-RIC

Busulfan/Thiotepa

Any allograft conditioning that includes full dose total body irradiation (TBI)

Any cord blood transplant

Patients who are treated for VOD should continue ursodeoxycholic acid until Day +100. All others should stop on discharge.

6.3. Diagnosis

In many cases the diagnosis of VOD is essentially clinical.
The classical symptoms are:

- Painful hepatomegaly
- Rapid unexplained weight gain (>5%)This is often an early sign
- Jaundice (bilirubin >34mmol/l)
- Peripheral oedema and ascites with third-spacing which is not responsive to diuresis
- Although not in the diagnostic criteria, severe platelet refractoriness is very commonly seen

Not all features may be present and the severity can vary. Historically, two groups defined the criteria for the clinical diagnosis of VOD. According to the Seattle criteria, VOD is diagnosed if there are 2 out of 3 clinical manifestations (jaundice, painful hepatomegaly and fluid retention). The Baltimore criteria allow a diagnosis of VOD when there is a bilirubin >34 umol/l together with 2 out of 3 clinical signs

(hepatomegaly, ascites and 5% weight gain). Both of these classifications required symptoms to commence within 21 days of transplant. However there was increasing evidence of “later onset” VOD, particularly in patients undergoing haplo-identical transplantation. Therefore EBMT in 2016 released new criteria for the diagnosis of VOD, splitting the diagnosis between Classical VOD and late onset VOD. Updated Clinical commissioning policy in April 2021 removed the requirement for onset of symptoms to be within the first 21 days of transplantation and followed the diagnostic criteria as per EBMT guidance. Therefore patients are eligible if the meet either the modified Seattle or Baltimore criteria or the EBMT late on set criteria.

6.4. Investigations

All patients suspected to have developed VOD should have **daily**:

- Weight measurement
- FBC
- Biochemistry
- Complete liver chemistry
- Clotting screen

6.4.1 Other useful investigations are:

- Abdominal ultrasound.
  Findings suggestive of VOD include ascites, hepatomegaly, gallbladder wall thickening,
  reversal of flow in the portal vein, abnormal portal wave form and
  a hepatic artery index >0.75.
- Liver biopsy:
  Generally liver biopsy is not required unless there is significant diagnostic uncertainty, as typically clinical diagnosis is sufficient. Should biopsy be required, it must always be done via a transjugular approach to minimise the risk of bleeding (still around 20%). If possible, during the catheterisation, the portal-hepatic venous gradient should be measured (if greater than 10mmHg, it has a specificity of 91% and a positive predictive value of 86%) Discussion between a Haematology and Hepatology Consultant is mandatory before undertaking this procedure.

6.5. Treatment

There are no therapies other than defibrotide that have conclusively proven to be effective in the management of VOD. Special consideration should be given to an adequate fluid balance and avoiding intravascular volume depletion.

Treatment should be started immediately VOD is clinically suspected as there is evidence for superior outcomes if defibrotide is started earlier.

Defibrotide is ONLY funded by NHS England if patient meets the modified Baltimore/Seattle criteria below or the EBMT criteria for late onset SOS/VOD

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

Classical SOS/VOD	Late onset SOS/VOD
• In the first 21 days after HSCT • Bilirubin ≥2 mg/dL and two of the following criteria must be present: ○ Painful hepatomegaly ○ Weight gain >5% OR ○ Ascites	• ≥21 Days after HSCT • Classical VOD/SOS beyond day 21 OR • Histologically proven SOS/VOD OR • Two or more of the following criteria must be present: ○ Bilirubin ≥2 mg/dL (or 34 µmol/L) ○ Painful hepatomegaly ○ Weight gain >5% ○ Ascites AND • haemodynamical or/and ultrasound evidence of SOS/VOD
Abbreviations: EBMT = European Society for Blood and Marrow Transplantation; SOS = sinusoidal obstruction syndrome; VOD = veno-occlusive disease. These symptoms/signs should not be attributable to other causes.	

Source: NHS England 210401PClinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease following stem cell transplant (Revised) April 2021

Grading should be undertaken as per the following EBMT criteria:

	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) Bilirubin (µmol/L)	⩾2 and <3 ⩾34 and <51	⩾3 and <5 ⩾51 and <85	⩾5 and <8 ⩾85 and <136	⩾8 ⩾136
Bilirubin kinetics			Doubling within 48 h	
Transaminases	⩽2 × normal	> 2 and ⩽5 × normal	>5 and ⩽8 × normal	>8 × Normal
Weight increase	< 5%	⩾5% and <10%	⩾5% and <10%	⩾10%
Renal function	<1.2 × baseline at transplant	⩾1.2 and <1.5 × baseline at transplant	⩾1.5 and <2 × baseline at transplant	⩾2 × baseline at transplant or others signs of MOD/MOF

Abbreviations: EBMT = European society for Blood and Marrow Transplantation; MOD = multi-organ dysfunction; MOF = multi-organ failure; SOS = sinusoidal obstruction syndrome; VOD = veno-occlusive disease. Patients belong to the category that fulfills two or more criteria. If patients fulfill two or more criteria in two different categories, they must be classified in the most severe category. Patients weight increase ⩾5% and <10% is considered by default as a criterion for severe SOS/VOD; however, if patients do not fulfill other criteria for severe SOS/VOD, weight increase ⩾5% and <10% is therefore considered as a criterion for moderate SOS/VOD. [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 very severe. [c]Time from the date when the first signs/symptoms of SOS/VOD began to appear (retrospectively determined) and the date when the symptoms fulfilled SOS/VOD diagnostic criteria.

Source: Revised diagnosis and severity criteria for SOS/VOD in adult patients. Bone Marrow Transplantation (2016) 51, 906-921, doi:10.1038/bmt2016.130

6.5.1. Initial Management

– the following are the current recommendations in our unit:

Defibrotide: IV 25mg/kg/day in 4 divided doses (i.e. 6.25mg/kg qds)

Dilute with sodium chloride 0.9% to a concentration in the range of 4mg in 1ml to 20mg in 1ml. Infuse over 2 hours using an infusion set with a 0.2micron or equivalent in-line filter. Give via an infusion pump

Note: A Blueteq form must be submitted within 48 hours of commencing defibrotide.

Duration of Treatment

Defibrotide should be administered for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve.

Escalation of Treatment

If no response to treatment, or in the event of further deterioration, **the dose may be increased to 40mg/kg/day in discussion with Consultant** (administered as above).

Side effects of Defibrotide include dizziness, nausea and vomiting, diarrhoea, flushing, and hypotension.

Contraindication - Defibrotide should NOT be used if there is clinical bleeding.

6.5.2. Other Measures

- Fluid restriction : use higher concentrated potassium to treat hypokolaemia if required
- Hyperdiuresis: IV Frusemide; Spironolactone
- Maintain intravascular volume; consider human albumin solution (HAS 20%)
- Keep haemoglobin level above 10g/dl
- Aim for higher platelet level (>30) if possible, though platelet refractoriness is common in these patients (and often an early sign of impending VOD)
- Dose adjust nephrotoxic and hepatotoxic drugs, especially Cyclosporin A
- Consider early referral to the renal and hepatology departments.
- Patients with severe VOD or not responding to initial measures and developing hepato-renal syndrome should be considered as candidates for early haemofiltration.
- Consider continuing IV treatment for 1-2 weeks depending on response and then consider switching to oral for further 1-2 weeks.

6.5.3. Second-line therapy– *the following measures may be considered:*

- Steroids can be used at Consultant discretion

7. Limitations of Procedure

7.1. Endpoint and Expected Results

Appropriate investigations, diagnosis and treatment of VOD.

7.2. Limitations

7.2.1. A Blueteq form (individual funding request) is required for each patient treated.

7.2.2. Adverse incidents must be reported via the NUH Trust Datix system

8. Audit

8.1. Incident reports will be reviewed at Departmental Governance meeting and the BMT Quality Management Group

8.2. NHS England require regular audit on the use of defibrotide which will be undertaken by High Cost Medicines Management team in Pharmacy with assistance from the BMT Quality Manager. Audit criteria will encompass the following:

- The percentage of patients undergoing allogeneic transplantation who receive defibrotide treatment and outcomes.
- Patients receiving defibrotide to demonstrate compliance with commissioning criteria.

9. Evidence Base of Policies / References:

- BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. British Journal of Haematology, **2013**, 163, 444–457
- Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation
  Bone Marrow Transplantation (2016) 51, 906–912
- NHS England 210401PClinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease following stem cell transplant. (Revised April 2021)
  Available at: Use-of-defibrotide-in-severe-veno-occlusive-disease-following-stem-cell-transplant-all-ages.pdf (england.nhs.uk)
- NUH Trust Medicines Code of Practice –Medicines Financial Control Policy CL/MM/035, available at http://nuhnet/nuh_documents/Documents/Medicines%20Financial%20Control%20Policy.doc
- PL6 Bone Marrow Transplant Programme Operational Policy and Quality Manual for Nottingham University Hospitals NHS Trust BMT Programme.
- FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration , Edition 8
  - available at https://www.ebmt.org/jacie-accreditation

10. Training and Competency:

Clinical Guidelines are “policy and/or guideline” documents. They do not require a competency, but still require a record that staff have read the document.
Once they have read the SOP, nursing and consultant staff members are required to log into QPulse and acknowledge the in use version.

Registrars are required to complete a read list on rotating to Fletcher ward, and sign off for this SOP on that document.