Management of Hepatic Veno-occlusive Disease (VOD)

Background

Hepatic veno-occlusive disease (VOD) or sinusoidal obstructive syndrome (SOS) is a disorder characterised by obstruction of small intra-hepatic venules and damage to the surrounding centrilobular hepatocytes and sinusoids. It occurs principally as a complication of chemo-irradiation therapy, particularly following BMT. The pathophysiological process leads to the clinical syndrome of weight gain, ascites, painful hepatomegaly and jaundice, with multi-organ failure (MOF) in severe cases. The incidence of SOS/VOD varies with the intensity of the conditioning regimen, the type of transplant and the presence of risk factors, but at present is 10-15% after allogenic transplant with myeloablative conditioning, compared with <5% after autologous/RIC conditioning. The most severe forms are associated with a high mortality rate (>80%).

Risk Factors

Risk factors include transplant-related, patient and disease-related and hepatic-related factors;

<u>Transplant-related</u>
- Unrelated, HLA mismatched, second HCT
- Myeloablative conditioning, oral or high-dose busulfan-based regimen, high-dose TBI
- Non T-cell depleted transplant

<u>Patient and disease-related</u>
- Older age
- Karnovsky sore <90%
- Female receiving norethisterone
- Advanced disease
- Thalassemia, high ferritin >2000

<u>Hepatic-related</u>
- Transaminases >2.5 ULN
- Serum bilirubin >1.5 ULN
- Cirrhosis
- Active viral hepatitis
- Abdominal or hepatic irradiation
- Hepatotoxic drugs
- Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin
- Iron overload

Diagnosis

VOD is usually a clinical diagnosis. VOD is defined (on the EBMT criteria for SOS/VOD in adults which are based on the Baltimore criteria below) as below:

Classical SOS/VOD in the first 21 days after HSCT	Late onset SOS/VOD >21 days after HSCT
Bilirubin ≥ 34 micromol/L plus **two** of the following: • Hepatomegaly • Weight gain >5% • Ascites	Classical VOD beyond day 21 **OR** Histologically proven SOS/VOD **OR** Two or more of the following: • Bilirubin ≥ 34 micromol/L • Painful hepatomegaly • Weight gain >5% • Ascites AND Haemodynamical and/or ultrasound evidence of SOS/VOD

Differential Diagnosis

Infections (CMV/adenovirus)
Drug toxicity
Hepatitic GVHD
Congestive cardiac failure leading to hepatic obstruction

Investigations (mainly to exclude other causes)

- Liver function tests
- Creatinine, Urea and electrolytes
- PT, APTT and Fibrinogen
- Ultrasound including Doppler studies (not usually diagnostic, but can exclude other causes of hepatic impairment and confirm ascites)
- CMV/Adenovirus PCR
- Transvenous liver biopsy

NB. Percutaneous liver biopsy, in patients with platelet counts < 60 x 10^9/l has an unacceptable risk of bleeding. The risk/benefit analysis of liver biopsy should be carefully considered and appropriate treatment not delayed when considering biopsy.

EBMT criteria for severity grading of a suspected SOS/VOD				
	Mild	**Moderate**	**Severe**	**Very severe**
Time since clinical onset (days)	**>7**	**5-7**	**⩽4 Days**	**Any time**
Bilirubin (µmol/L) *Kinetics*	**⩾34 and <51**	**⩾51 and <85**	**⩾85 and <136** *Doubling within 48 h*	**⩾136**
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**	**⩾1.2 and<1.5 × baseline**	**⩾1.5 and <2 × baseline**	**⩾2 × baseline or other signs MOF**

Prophylaxis

All patients at risk of VOD must receive: Oral Ursodeoxycolic acid 300 mg PO BD (<90 kg) or 450mg BD for patients (>90 kg), until day + 30 post-transplant or discharge home whichever is the latest (BCSH guidelines 2013, Cochrane Review 2015).

Treatment

The mainstay of treatment is supportive management with careful fluid balance, and judicious use of diuretics. Patients may also require treatment with defibrotide; this should be discussed with the consultant.

Supportive care

- Twice daily weight and fluid balance.
- Nutritonal support, preferably enteral (parenteral nutrition is associated with fluid overload, infectious complications, and hepatotoxicity, and should be avoided)
- Daily renal and liver function testing.
- Diuresis (furosemide and/or spironolactone).
- Withold nephrotoxic/hepatotoxic drugs.
- Oxygen therapy/therapeutic drainage of massive ascites/symptomatic pleural effusions.
- In patients with severe renal dysfunction, hemodialysis/hemofiltration is required.
- Early discussion with critical care specialists and hepatology are recommended in severe cases.
- The usefulness of transjugular intrahepatic portosystemic shunt is limited to symptomatic control, with no benefit on survival

Defibrotide

Defibrotide is the agent with proven efficacy for the treatment of VOD/SOS and is usually indicated for treatment of severe, or moderate VOD/SOS if not responding to supportive measures or those who have rapidly rising weight or bilirubin (2x or 3x over 24 hours. The latter fall into a poor prognosis group, with a mortality of upwards of 50%. Given the mortality associated with severe and very severe SOS/VOD, it is mandatory to treat these patients

promptly, and DF should be initiated as soon as possible. Defibrotide should be continued until the bilirubin level has normalized.

Funding: Defibrotide is routinely commissioned in patients who have a diagnosis of severe veno-occlusive disease following BMT based on clinical criteria (modified Seattle or Baltimore criteria) or histopathological findings.

Requires BLUETEQ application (if a Bluteq form cannot be completed due to logistical reasons, treatment must not be delayed, the form must be completed subsequently retrospectively at the earliest opportunity- agreed with NHSE pharmacist).

Dosing and administration:

Dose	Defibrotide 6.25mg/kg QDS every SIX hours (i.e.25mg/kg/day in four divided doses) It is not recommended to dose above 25 mg/kg/day.
Dose adjustments	**Renal impairment/haemodilysis**: No dose adjustment required **Hepatic impairment**: No dose adjustment is required. Monitor closely.
Method of Administration	**IV infusion**: Give as an intravenous infusion over 2 hours using an infusion set with a **0.2microns** or equivalent in-line filter.
Dilution	Dilute with sodium chloride 0.9% or glucose 5% to a final concentration in the range of 4 mg/mL to 20 mg/mL**. Follow the injectable monograph for further administration details. **If fluid restricted, use minimum possible dilution fluid volume.
Treatment Duration	The treatment should be administered for a minimum of 21 days (occasionally earlier) and continued until the symptoms and signs of VOD resolve
Adverse Events	Generally mild but the following reported • Active bleeding (ca. 50% of patients) • Hypotension (ca. 25% of patients) • A sensation of generalised heat if administered rapidly • Rare instances of dizziness, nausea, vomiting & diarrhea, all abating spontaneously • Flushing, headache and allergic reactions have occasionally been reported

<u>Management of haemorrhagic risk with Defibrotide</u>

For invasive procedures, in addition to platelet transfusions, DF should be suspended at least 2 h before and 2 h after the procedure, given its relatively short half-life (<2 h). For patients with life-threatening bleeding, DF must be immediately discontinued, and its resumption should be discussed on a case per case basis and according to the risk/benefit ratio.

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Audit

These processes are subject to the OxBMT audit programme

Circulation

NSSG Haematology Website

Review

Name	Revision	Date	Version	Review date
Dr Andy Peniket, BMT Programme Director	Minor	May 2011	3.1	May 2013
Prof. Vanderson Rocha, Consultant Haematologist	Full review	Oct 2014	4.0	Oct 2016
Dr Andy Peniket, BMT Programme Director Sandy Hayes, Quality Manager	Ferritin assessment, Fragmin from admission to Day 0, BSCH reference.	July 2015	4.1	Oct 2016
Dr Andy Peniket, BMT Programme Director Sandy Hayes, Quality Manager Dr Mimi Sheikh, Specialist Haematology Reg	Full review and discontinuation of heparin and fragmin for patients at risk. Cochrane review reference.	Nov 2015	5.0	Nov 2017
Cheuk-Kie Cheung, Specialist Cancer Pharmacist	Update with dose, renal adjustment and supplier, reference	Feb 2017	5.1	Feb 2019
Andy King, Haematology registrar Nadjoua Maouche, Lead Haematology pharmacist Cristina Ovas, BMT Quality and Data Manager	Protocol review day Diagnosis. Criteria. Dosing and administration. Update Defibrotide funding and BLUTEQ requirement. References	July 2019	6.0	July 2021
Gavinda Sangha, Haematology Registrar Nadjoua Maouche, Lead Haematology pharmacist Cristina Ovas, Quality and Data Manager	Protocol review day. Risk factors, Investigation, Prophylaxis and Treatment	April 2022	7.0	April 2024