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 reported incidence of VOD post BMT is 20% after myeloablative conditioning, with a mortality of up to 50%; after reduced intensity conditioning the incidence of VOD varies from 3 to 9%. The most severe forms result in multi-organ failure, and are associated with a high mortality rate (>80%).

Risk Factors
Risk factors for the development of VOD, and patients who should be considered for VOD prophylaxis are as follows:
- Pre-transplant elevated transaminases, 1.5x baseline levels
- Persistent fever during cytoreductive therapy
- Second HSCT
- Pre-existing hepatic disease
- Mismatched donor transplants (also included Haplo and Cord)
- previous treatment with chemotherapy regimens containing: Mylotarg (gemtuzumab ozogamicin) or Inotuzumab ozogamicin.
- Myeloablative conditioning regimen
- Busulphan as part of conditioning regime
- High ferritin levels (>2000)

Screening of Ferritin levels commences at first BMT consultation and levels are monitored up to BMT admission.

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).
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:

<table>
<thead>
<tr>
<th>Classical SOS/VOD in the first 21 days after HSCT</th>
<th>Late onset SOS/VOD &gt;21 days after HSCT</th>
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<tbody>
<tr>
<td>Bilirubin ≥ 34 micromol/L plus two of the following:</td>
<td>Classical VOD beyond day 21 OR Histologically proven SOS/VOD OR Two or more of the following:</td>
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<tr>
<td>• Heptaomegaly</td>
<td>• Bilirubin ≥ 34 micromol/L</td>
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<td>• Weight gain &gt;5%</td>
<td>• Painful hepatomegaly</td>
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<tr>
<td>• Ascites</td>
<td>• Weight gain &gt;5%</td>
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<tr>
<td>AND Haemodynamical and/or ultrasound evidence of SOS/VOD</td>
<td>• Ascites</td>
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</table>

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
- 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.
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. Early discussion with critical care specialists and hepatology are recommended in severe cases. No treatments aside from defibrotide have a strong evidence base.

Defibrotide

The indication for Defibrotide should be assessed on an individual patient basis. Generally, patients not responding to supportive measures or those who have rapidly rising weight or bilirubin (2x or 3x over 24 hours) should be considered. The latter fall into a poor prognosis group, with a mortality of upwards of 50%. 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:

<table>
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<tr>
<th>Dose</th>
<th>Defibrotide 6.25mg/kg QDS every SIX hours (i.e. 25mg/kg/day in four divided doses)</th>
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<td>Note: individual doses should be rounded to the nearest vial (vials come as 200mg/2.5ml). It is not recommended to dose above 25 mg/kg/day.</td>
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<tr>
<th>Dose adjustments</th>
<th>Renal impairment/haemodilysis: No dose adjustment required</th>
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<tbody>
<tr>
<td>Hepatic impairment:</td>
<td>No dose adjustment is required. Monitor closely.</td>
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</table>

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 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
**Fluid balance and ascites**
1. Patients with ascites should be sodium +/- fluid restricted. Plasma volume should be maintained with plasma expanders rather than saline.
2. A small daily negative sodium balance should be the aim. Careful use of loop diuretics to achieve a urinary sodium excretion of >20mmol/l if possible.
3. Daily or twice daily weight and fluid balance control is essential.
4. Abdominal girth measurement can be considered.

**Encephalopathy**
1. Avoid gastrointestinal nitrogen load by prompt treatment of intra-luminal haemorrhage.
2. Avoid sedatives and opiate analgesia
3. Correct known precipitants of encephalopathy such as hypokalaemia, constipation and infection.

**Hepatic synthetic function**
1. Monitor blood glucose
2. Daily check of prothrombin time and APTT and correct with FFP as necessary

**Renal function**
1. Avoid nephrotoxic drugs whenever possible, particularly amphotericin aminoglycosides. Avoid toxic ciclosporin levels

**Other treatment options:**
- Methylprednisolone: 0.5mg/kg BD iv for 14 days (BCSH guidelines 2013)
- Recombinant tissue-plasminogen activator (tPA) and heparin
- Prostaglandin E1 has both vasodilator and antiplatelet activity
- Glutamine and Vitamin E function as antioxidants
- TIPS, Protein C replacement
- Surgical shunt or liver transplant

Early discussion with critical care specialists and hepatology are recommended in severe cases. No treatments aside from defibrotide have a strong evidence base.
References

10. Richardson PG et al. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno occlusive disease and multi organ failure: response without significant toxicity in a high risk population and factors predictive of outcome. Blood 2002; 100; 4337-4343
12. BCSH Guidelines, Veno-Oclusive Disease, 2013. BCSH/BSBMT guideline: Diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation.

Authors
Tim Littlewood, BMT Programme Director – Original and Version 2, 2004
Claire Humphries, Specialist Pharmacist – Original and Version 2, 2004
Ram Malladi, MRC Clinical Research Fellow and Honorary Specialist Registrar – Version 3, 2008
Denise Wareham BMT Co-ordinator – Amendments, 2009

Audit
These processes are subject to the OxBMT audit programme

Circulation
NSSG Haematology Website
## Review

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
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<td>Dr Andy Peniket, BMT Programme Director</td>
<td>Minor</td>
<td>May 2011</td>
<td>3.1</td>
<td>May 2013</td>
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<td>Dr Andy Peniket, BMT Programme Director</td>
<td>Ferritin assessment, Fragmin from admission to Day 0, BSCH reference.</td>
<td>July 2015</td>
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<td>Dr Andy Peniket, BMT Programme Director</td>
<td>Full review and discontinuation of heparin and fragmin for patients at risk. Cochrane review reference.</td>
<td>Nov 2015</td>
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<td>Nov 2017</td>
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<td>Cheuk-Kie Cheung, Specialist Cancer Pharmacist</td>
<td>Update with dose, renal adjustment and supplier, reference</td>
<td>Feb 2017</td>
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<td>Feb 2019</td>
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<td>Nadjoua Maouche, Lead Haematology pharmacist</td>
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<td>Cristina Ovas, BMT Quality and Data Manager</td>
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