Management of Hepatic Veno-occlusive Disease (VOD)

Definition
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%, with a mortality of up to 50%; after reduced intensity conditioning the incidence of VOD varies from 3 to 9%.

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
- mismatched donor transplants (also included Haplo and Cord)
- previous treatment with chemotherapy regimens containing Mylotarg
- 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: Oral Ursodeoxycolic acid 300 mg po bd (<90 kg) or 450mg bd for patients (>90 kg), until day + 30 post-transplant or discharge home (BCSH guidelines 2013, Cochrane Review 2015).

Diagnosis of VOD
VOD is usually a clinical diagnosis. VOD is defined (on the Baltimore criteria) as the onset before day 21 post BMT of:

- bilirubin >34micromol/l plus two of the following
  - hepatomegaly
  - ascites
  - weight gain > 5% from baseline
Where there is no other identifiable cause of liver disease.

Investigations
- Liver function tests
- Urea and electrolytes
- PT, APTT and Fibrinogen
- Ultrasound (not usually diagnostic, but can exclude other causes of hepatic impairment)
- CMV PCR
Transvenous liver biopsy

NB. Percutaneous liver biopsy, in patients with platelet counts < 60 x 10^9/l has an unacceptable risk of bleeding.

**Treatment**
The mainstay of treatment is the supportive management of fluid balance, renal failure and hepatic function. Some patients may require treatment with defibrotide; this should be discussed with the consultant.

**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

**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 should be considered. The latter fall into a poor prognosis group, with a mortality of upwards of 50%.

*Funding* for Defibrotide should be applied for on an individual patient basis, and a Blueteq application form will have to be filled in.

- **Dose:**
  - 25mg/kg/day IV in 4 divided doses
  - For adults > 50kg round dose to nearest 100mg

- **Available as:**
  - 200mg in 2.5ml (concentration 80mg/ml)
Administration: Dilute in 50ml glucose 5% or 0.9% sodium chloride (concentration range 4mg/ml to 20mg/ml) and infuse over 2 hours

Cautions/Side effects: 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 & diarrhoea, all abating spontaneously
- Flushing, headache and allergic reactions have occasionally been reported

Supply: Named Patient drug: available from Jazz Pharmaceuticals – takes 3 working days for delivery

Treatment period: Minimum 21 days, then review. Treat until CR or VOD progression or unacceptable toxicity.

Renal impairment: Dose adjustment is not required for patients with renal impairment or who are on intermittent haemodialysis.

Other 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

References
7. 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. Gentium SPA. SPC Defitelio 80mg/mL concentrate for solution for infusion. May 2016.

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

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<td>Minor</td>
<td>May 2011</td>
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<tr>
<td>Dr Andy Peniket, BMT Programme Director Sandy Hayes, Quality Manager</td>
<td>Ferritin assessment, Fragmin from admission to Day 0, BSCH reference.</td>
<td>July 2015</td>
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<tr>
<td>Dr Andy Peniket, BMT Programme Director Sandy Hayes, Quality Manager Dr Mimi Sheikh, Specialist Haematology Reg</td>
<td>Full review and discontinuation of heparin and fragmin for patients at risk. Cochrane review reference.</td>
<td>Nov 2015</td>
<td>5.0</td>
<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>Cheuk-Kie Cheung, Specialist Cancer Pharmacist</td>
<td>Defibrotide dilution concentration updated</td>
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