Hepatic Veno-Occlusive Disease (VOD)
Paediatric Haematology and Oncology Patients

This document should act as a guideline on the initial management of a child or young person with Hepatic Veno-Occlusive Disease within the Paediatric Haematology and Oncology unit, Oxford Children’s Hospital, Thames Valley Children’s Cancer Network.

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1.0 Introduction:

- The primary injury in VOD (Veno-Occlusive Disease) / SOS (Sinusoidal Obstructive Syndrome) is most likely a lesion of the sinusoidal endothelial cells of hepatic venules.

- In our unit, it most commonly occurs following a high dose chemotherapy regimen that contains Busulphan. It can also occur (although rarely) following Actinomycin D (Dactinomycin) therapy, particularly in patients with Wilms Tumour receiving preoperative chemotherapy.

- It is characterised by a clinical syndrome of tender hepatomegaly, jaundice, fluid retention, ascites and weight gain in an appropriate clinical setting.

- The risk of developing VOD following a Busulphan containing high dose chemotherapy regimen is quoted as 5-10%.

- VOD always needs prompt diagnosis and appropriate management as if severe and left untreated it can lead to portal hypertension, hepato-renal syndrome, multi organ failure and death.

2.0 Pathogenesis

The hepatic metabolism of certain drugs (i.e. Cyclophosphamide) by the cytochrome P-450 enzymatic system produces toxic metabolite (i.e. acrolein). These toxic...
metabolites are converted to non-toxic products by the glutathione enzymatic system (GSH) and eliminated. When this process happens in someone with a reduced GSH, due either to pre-existing liver disease, or to the action of agents that reduces GSH (i.e. Busulphan, Carmustine or irradiation), toxic damage to sinusoidal endothelium occurs leading to VOD/SOS\(^1\). Experimental models have shown that toxic damage of sinusoidal endothelium leads to downstream micro-embolism, causing sinusoidal blockade and reduced hepatic venous flow. This process produces post-sinusoidal hypertension, hence the proposed alternative name Sinusoidal Obstruction Syndrome (SOS).

3.0 Risk factors

- Chemotherapy agents
  - Busulphan
  - Actinomycin D (Dactinomycin)\(^{1,2,3}\)
  - Cyclophosphamide
  - Thioguanine\(^4\)
  - Carmustine
  - Gemtuzumab (Mylotarg)

- Previous hepatic irradiation / abdominal irradiation / total body irradiation (TBI)

- Pre-existing liver disease: tumour involvement, viral hepatitis, fatty degeneration, chemotherapy induced liver damage, (alcohol abuse)

- Current or previous deranged hepatic function

- Iron overload

- Other hepato-toxic drugs: Azole antifungals, Cyclosporin A, Amphotericin B, Aciclovir (often given prophylactically post stem cell reinfusion), Methotrexate, Intravenous Immunoglobulin (IVIG), Total Parenteral Nutrition (TPN)

- Norethisterone (often given in our unit for prevention of menstrual bleeding)

- Second transplant

4.0 Diagnosis

In most cases the diagnosis of VOD is clinical.

The classic symptoms are

I. Bilirubin >34 micromol/L (2mg/dl)
II. Painful hepatomegaly
III. Rapid weight gain >5% of basal body weight (usually secondary to ascites)
IV. Peripheral oedema and ascites

Other clinical features may include

- Thrombocytopenia and refractoriness to platelet transfusion

**NOTE: If this occurs in association with Actinomycin D (Dactinomycin) treatment, VOD MUST be considered**

- Pleural effusion
- Pulmonary infiltrate
- Progressive renal, cardiac and pulmonary failure
- Confusion, encephalopathy and coma

Two international groups have defined criteria for the clinical diagnosis of VOD: Baltimore and Seattle. For link to both criteria see: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cmed.table.40157

- Seattle criteria: VOD diagnosed if there are 2 out of 3 clinical symptoms (jaundice, painful hepatomegaly and fluid retention)

- Baltimore criteria: VOD diagnosed if Bilirubin is >34mmol/L (together with 2 out of 3 clinical symptoms (hepatomegaly, ascites and 5% weight gain)

**This unit will follow the Baltimore criteria**

Differential diagnosis to be considered
- Infections – e.g. viral hepatitis, especially adenovirus
- Fluid overload / renal failure
- Congestive heart failure / constrictive pericarditis
- Pulmonary arterial hypertension (PAH) leading to right heart failure & hepatomegaly (this may be accompanied by tachy or bradycardias, sudden desaturation episodes, panic attacks)
- Drug toxicity / Total Parenteral Nutrition (TPN)
- Hepatic Graft versus host disease (GVHD) (this can occur without preceding skin or gut GVHD)

5.0 **Investigations**

1. Full blood count
2. Clotting profile
3. Urea & Electrolytes, creatinine
4. Liver function tests
5. Infection screening including screening for EBV, Adenovirus and CMV
6. Abdominal ultrasound scan with dopplers – findings are non specific but common abnormalities seen include hepatomegaly, gall bladder wall thickening (also seen in infectious mononucleosis, post transplant lymphoproliferative disorder (PTLD) and haemophagocytic lymphohistiocytosis (HLH), ascites and decreased or reversed portal flow
7. Echocardiogram (ECHO) to exclude cardiac causes and pulmonary arterial hypertension.

6.0 **Management**

**Prophylaxis**
- Ursodeoxycholic acid can be used as prophylaxis in high risk patients e.g. Busulphan High Dose Chemotherapy. However it is now not recommended in the SIOPEN HR NBL protocol.
- There is no funding (national decision as of Nov 2015) for Defibrotide to be used prophylactically in solid tumour patients at risk of VOD.

**Identify children at high risk of developing VOD**
- Minimise other hepato-toxic factors to decrease the risk of VOD
- Inform pharmacy prior to a patient at risk of developing VOD starting their High Dose treatment to ensure that there can be defibrotide available if needed.
- Current recommendations include the use of intravenous Busulphan instead of oral Busulphan, and withholding routine antifungal prophylaxis post high dose – then using liposomal amphotericin rather than azole antifungals if suspicion of fungal disease arises.
Active management
Initial / symptomatic management
- Strict monitoring of fluid balance – input / output charting
- Twice daily body weight
- Restriction of salt and water intake
- Adequate diuresis and maintenance of an adequate urine output (>3mls/kg/hr)
- Use Furosemide either as a bolus or continuous infusion
- Maintain intravascular volume and renal perfusion using transfusions (keep haematocrit >30%), albumin and plasma expanders
- Correct deranged clotting
- Keep platelets >50
- Dose adjust nephritic and hepato-toxic drugs
- Defibrotide should be started urgently if VOD suspected after discussion with the Consultant in charge
- Contact the Paediatric Haematology/Oncology pharmacist or on-call pharmacist if you are considering using defibrotide – the product is very expensive and available on special order only. It is unlicensed and imported, and the consultant must sign a special request form in order for pharmacy to obtain the drug. A small supply may be available on site to start a patient over a weekend or overnight. In some cases another hospital may be contacted to help with supplies.
- Inform the Critical care team of patient
- Consider transfer to HDU/PICU
- Discuss the need for the use of inotropes if indicated with intensive care specialists
7.0 Useful drug doses

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<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>FREQUENCY</th>
<th>NOTES</th>
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<tr>
<td>Defibrotide (treatment dose)</td>
<td>6.25-10 mg/kg</td>
<td>Intravenous infusion over 2 hours 6 hourly for 10-14 days</td>
<td>Note Defibrotide is derived from porcine mucosal DNA. Consider need for consent from Muslim or Jewish patients</td>
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<tr>
<td>Ursodeoxycholic acid</td>
<td>10 mg/kg/day</td>
<td>In one or two divided doses</td>
<td>SIOPEN HR NBL protocol recommends 150mg/m²/day in 2 divided doses</td>
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<tr>
<td>Furosemide</td>
<td>0.5-1.0 mg/kg</td>
<td>IV bolus every 8 hours</td>
<td>Maximum dose 2mg/kg/hour</td>
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<td>Furosemide infusion⁶</td>
<td>0.1-2 mg/kg/hour</td>
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8.0 References / Associated documentation

There are 2 important recent documents about VOD which contain supporting and additional information on VOD

Clinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease following stem cell transplant
https://www.england.nhs.uk/commissioning/.../b04-use-defibrotide.pdf

BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation.


Other references

5) Lee JH. Hepatic veno-occlusive disease (VOD) after allogeneic hematopoietic cell transplantation (HCT) in adults conditioned with Busulphan (Bu) and Cyclophosphamide (Cy) at a single centre: A retrospective comparison of oral vs. intravenous Bu. JCO, ASCO Annual Meeting Proceeding (Post-Meeting Edition), Vol 22, NO 14s (July 15 Supplement), 2004: 66472004
6) Children’s BNF, 2015

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<td>Dr Kate Wheeler, Paed Oncology Consultant and Pharmacy team</td>
<td>New doc</td>
<td>Jan 2012</td>
<td>1.0</td>
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<td>Dr Kate Wheeler, Paed Oncology Consultant and Pharmacy team</td>
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