SOUTHAMPTON Children's Hospital

# Wessex Paediatric Oncology Supportive Care Guidelines: Management of Veno-Occlusive Disease.

**Scope**
This guideline applies to all paediatric oncology patients in the region. It does not apply to neonates on neonatal units.

**Purpose**
Children receiving treatment at the Southampton Paediatric Oncology Principal Treatment Centre (PTC) have open access to the designated Paediatric Oncology Ward at either the PTC or their Paediatric Oncology Shared Care Unit (POSCU). Their parents/carers will be in possession of contact details for these wards and have been instructed to contact them for any medical problems that arise while they are receiving treatment. These Guidelines are intended for the use of the medical teams at the PTC or POSCU. If one of the Paediatric Oncology patients presents to a medical service outside of the PTC or POSCU, please contact the medical teams at the PTC or POSCU for advice.

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Adapted from TVCN Principal Treatment Centre Children's Hospital Oxford Guidelines on Hepatic VOD and National Child Centre Network Starship Child Health, New Zealand Hepatic VOD guideline

# Diagnosis and Management of Veno-Occlusive Disease

## 1.1 Introduction

Veno-occlusive disease (VOD) is a potentially life-threatening complication that mainly occurs after high dose myelo-ablative conditioning therapy and haematopoietic stem-cell transplantation (HSCT), usually occurring before day +30 after transplantation. The primary injury in VOD is most likely a lesion of the sinusoidal endothelial cells of hepatic venules which is why is it sometime referred to as SOS (Sinusoidal Obstructive Syndrome)

For paediatric oncology patients, it most commonly occurs following a high dose chemotherapy regimen that contains busulfan. It can also occur (although rarely) following Actinomycin D (Dactinomycin) therapy, particularly in patients with Wilms Tumour receiving chemotherapy or patients with rhabdomyosarcoma.

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 busulfan 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. Severe VOD is associated with a mortality rate of >90% by day +100 following HSCT.

## 1.2 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.

This process is less efficient in someone with a reduced GSH, due either to pre-existing liver disease, or to the action of agents that reduces GSH (i.e. Busulfan, Carmustine or irradiation), causing damage to the sinusoidal endothelium (due to increased exposure to the toxic metabolites of chemotherapy agents). Experimental models have shown that toxic damage of the 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). Portal hypertension in turn can lead to hepato-renal syndrome and multi-organ failure.

## 1.3 **Risk factors**

- Chemotherapy agents
  - Busulfan
  - Actinomycin D (Dactinomycin) [1 2 3]
  - Cyclophosphamide
  - Thioguanine [4]
  - Carmustine
  - Gemtuzumab (Mylotarg)

- Current or previous deranged hepatic function
- Pre-existing liver disease: tumour involvement, viral hepatitis, fungal infection affecting liver, fatty liver degeneration, chemotherapy induced liver damage, (alcohol abuse)
- Previous hepatic irradiation / abdominal irradiation / total body irradiation (TBI)
- Concurrent hepato-toxic drugs:
  - Azole antifungals, (itraconazole, fluconazole, voriconazole)
  - Ciclosporin
  - Amphotericin B (Ambisome)
  - Total Parenteral Nutrition (TPN)
  - Aciclovir (often given prophylactically post stem cell reinfusion)
  - Methotrexate
  - Intravenous Immunoglobulin (IVIG)
- Norethisterone (sometimes given in our unit for prevention of menstrual bleeding)
- Tranexamic acid
- Second transplant
- Iron overload

**Identify children at high risk of developing VOD**

For patients who have been identified as being high risk for developing VOD, ensure the following management:

- Strict monitoring of fluid balance – input / output charting
- Twice daily body weight and measuring of abdominal girth
- Adjust doses or minimise use of nephro-toxic and hepato-toxic drugs
- Inform pharmacist if a patient has been identified at high risk of developing VOD to ensure that defibrotide is available if needed.
- Current recommendations include the use of intravenous Busulfan instead of oral Busulfan, and withholding routine antifungal prophylaxis post high dose. If suspicion of fungal disease arises, liposomal amphotericin (Ambisome) should be used as first line therapy.

## 1.4 Diagnosis of hepatic veno-occlusive disease

In most cases the diagnosis of VOD is clinical. In the early stages, the classic symptoms (see below table) are often not present. Relative platelet refractoriness with a mild elevation of hepatic enzymes may be the only signs. VOD usually occurs within 30 days of transplant or within a week of receiving more conventionally-dosed chemotherapy.

Table 1.4 Classic symptoms of hepatic veno-occlusive disease

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

Other clinical features may include:

- Thrombocytopenia and refractoriness to platelet transfusion

**NOTE: If thrombocytopenia and refractoriness to platelet transfusion 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
- Sodium retention and decreased fractional excretion of sodium progressing to hepatorenal syndrome

Two international groups have defined criteria for the clinical diagnosis of VOD: Baltimore and Seattle.

| **Modified Seattle criteria[5]**<br><br>*Two of the following criteria must be present within 20 days of transplant:* | **Baltimore criteria[6]**<br><br>*Bilirubin must be >34·2 µmol/l (2 mg/dl) within 21 days of transplant and two of the following criteria must be present:* |
|---|---|
| Bilirubin >34·2 µmol/l (2 mg/dl)<br><br>Hepatomegaly or right upper quadrant pain<br><br>Weight gain (>2% from pre-transplant weight) | Ascites<br><br>Hepatomegaly<br><br>Weight gain (>5% from pre-transplant weight) |

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)

### 1.5 Investigations

1. Full blood count
2. Clotting profile
3. Urea & Electrolytes, creatinine, calcium, magnesium, phosphate
4. Liver function tests (including split bilirubin and albumin)
5. Infection screening including screening for EBV (Epstein-Barr virus), Adenovirus and CMV (Cytomegalovirus)
6. Abdominal ultrasound scan with dopplers – findings are non specific but common abnormalities seen include hepatomegaly, ascites and gallbladder wall thickening. While doppler ultrasound showing reversal of portal venous flow is diagnostic, it is usually only present at the late stages of the disease and its absence does not exclude VOD.
7. Echocardiogram (ECHO) to exclude cardiac causes and pulmonary arterial hypertension.

### 1.6 Management

**Prophylaxis**

Ursodeoxycholic acid is no longer recommended as prophylaxis for high risk patients receiving busulfan high dose chemotherapy and has been removed from the SIOPEN HR NBL protocol.

There is no national funding for the prophylactic use of defibrotide in solid tumour patients at risk of VOD. Individual patients considered to be of particular high risk of VOD will need to be discussed and an individual funding request (IFR) for prophylactic defibrotide can be made in exceptional circumstances.

Pharmacokinetic monitoring of busulfan levels can be arranged in particularly high risk patients. Dose modification may reduce the incidence of hepatic VOD.

**Treatment of hepatic VOD**
The mainstay of treatment of VOD includes supportive care, particularly the management of fluid balance and the use of defibrotide.

The total amount of fluids should be restricted and diuretic therapy should be administered in severe fluid overload.

**Fluid management**

- Strict monitoring of fluid balance – input / output charting
- Twice daily body weight and measuring of abdominal girth
- Restriction of sodium and water intake
- Minimal volume dilution of drugs and TPN – discuss with pharmacist
- If compatible, dilute drugs in 5% dextrose rather than 0.9% sodium chloride
- Adequate diuresis and maintenance of an adequate urine output (>3mls/kg/hr)
- Use furosemide either as a bolus or continuous infusion and/or spirinolactone
- Maintain intravascular volume and renal perfusion using transfusions (keep haematocrit >30%). Fluid balance may be hard to assess due to the fluid accumulation with VOD but aggressive diuretic therapy may deplete intravascular volume predisposing to sludging within hepatic sinusoids.
- For hypoalbuminaemia – consider giving 20% HAS after discussion with Consultant

**Clotting and platelets**

- Correct deranged clotting
- Try to maintain platelets >50 but note that platelet transfusions should be limited as supplementing platelets can increase sinusoidal obstruction

**Dose modification of drugs**

- Adjust doses of nephro-toxic and hepato-toxic drugs
- Modify TPN to ensure appropriate fat source used in liver impairment.

**Defibrotide**

- Defibrotide should be started urgently if VOD suspected after discussion with Consultant. See below.

**Other considerations**

- Inform the Outreach and PICU team of patient
- Consider transfer to HDU/PICU
- Discuss the need for the use of inotropes if indicated with intensive care specialists

## Defibrotide

Defibrotide has several modes of action including: antithrombotic, anti-inflammatory and anti-ischaemic and appears to have a protective effect against endothelial cell injury caused by chemotherapy drugs. It has demonstrated efficacy and safety in the treatment of VOD.

**Inform the Paediatric Haematology/Oncology pharmacist or on-call pharmacist if you are considering using it as it is very expensive and available on special order only.**

**Please refer to the NHSE commissioning policy: Clinical commissioning policy: Use of defibrotide in severe VOD following stem cell transplant. For any indication not included in the policy – an Individualised Funding Request (IFR) must be submitted.**

Contraindications for defibrotide treatment – (see summary of product characteristics for full details)

- Hypersensitivity to defibrotide (or excipients)
- Concomitant use of thrombolytic therapy (e.g. t-PA)

Caution is advised when using medicinal products that increase the risk of haemorrhage or anticoagulant therapy

Side-effects of defibrotide: High risk of haemorrhage, hypotension, vomiting, diarrhoea

## Table 1: Useful drug doses for VOD management[13]

| Drug | Route | Dosing information |
|---|---|---|
| **Defibrotide (treatment dose)** | IV | **Child > 1 month** 6.25mg/kg 6 hourly<br><br>Intravenous infusion over 2 hours<br>Defibrotide should be used for a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve.<br>Note defibrotide is derived from porcine mucosal DNA. Consider need for consent from Muslim or Jewish patients. |
| **Ursodeoxycholic acid** | PO | 10-15mg/ kg BD (total daily dose may alternatively be given in 3 divided doses) |
| **Spirinolactone** | PO | **Child 1month – 11 years**<br>Initially 1-3mg/kg daily in 1-2 divided doses; increased if necessary up to 9mg/kg daily<br><br>**Child 12-17years**<br>Initially 50-100mg daily in 1-2 divided doses; increased if necessary up to 9mg/kg daily (max. 400mg) |
| **Potassium Canrenoate** | IV | **Child 1month-11 years**<br>1-2mg/kg BD<br><br>**Child 12-17years**<br>1-2mg/kg BD (max. per dose 200mg) |
| **Furosemide** | IV Bolus | **Child 1 month – 11years**<br>0.5-2 mg/kg every 8-12 hours (max. 12mg/kg/day)<br><br>**Child 12-17 years**<br>20-40mg every 8 hours as required, higher doses may be required in resistant cases |
| | IV infusion | 0.1-2 mg/kg/hour<br>Maximum dose 2mg/kg/hour |

## 1.7 References & Further Reading

Important documents about VOD:

1. Clinical Commissioning Policy: Use of defibrotide in severe veno-occlusive disease following stem cell transplant
   Link: *https://www.england.nhs.uk/commissioning/.../b04-use-defibrotide.pdf*
2. BCSH/BSBMT guideline: Diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Dignan FL, Wynn RF, Hadzic N, Karani J, Quaglia A, Pagliuca A, Veys P, Potter MN; Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. Br J Haematol. 2013 Nov;163(4):444-57. doi: 10.1111/bjh.12558. Epub 2013 Sep 17

**References from guideline**


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2) Ortega JA. Veno-occlusive disease of the liver after chemotherapy with Vincristine, Actinomycin D and Cyclophosphamide for the treatment of rhabdomyosarcoma. Cancer 1997; 79 (12): 2435-9
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5) ) Shulman, H.M. & Hinterberger, W. (1992) Hepatic veno-occlusive disease–liver toxicity syndrome after bone marrow transplantation. *Bone Marrow Transplantation*, **10**, 197–214. (Seattle Criteria)
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9) Qureshi A et al. Defibrotide in the prevention and diagnosis of veno-occlusive disease in autologous and allogeneic stem cell transplant in children. Pediatr Blood Cancer 2008 Apr; 50 (4): 831-2
10) Dignan F et al. Prophylactic Defibrotide in allogeneic stem cell transplantation: minimal morbidity and zero mortality from veno-occlusive disease. Bone Marrow Transplant 2007; 40: 79-82
11) Richardson P, Soiffer R, Antin J, Jin Z, Kurtzberg J, Martin P et al. Defibrotide (DF) for the treatment of severe veno-occlusive disease (sVOD) and multi-organ failure (MOF) post SCT: final results of a multi-centre, randomised, dose finding trial. *Blood 2006; 108: 178*
12) Ho VT, Revta C, Richardson PG. Hepatic veno-occlusive disease after haematopoietic stem cell transplantation: update on Defibrotide and other investigational therapies. Bone marrow transplantation (2008) 41, 229-237
13) BNFC September 2017 available at https://www.medicinescomplete.com/mc/bnfc/current/. Accessed 05/10/17


**Link to parent information on VOD**

http://www.cclg.org.uk/write/MediaUploads/Publications/PDFs/Veno_occlusive_disease_(Mar_14).pdf

# "Management of Veno-occlusive disease in Paediatric Oncology patients"

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| **Signature of ratifying Group Chair** | Juliet Gray |
| **Author's and job titles** | Dr Jessica Bate: Paediatric Oncology consultant<br>Claire Fosbrook: Paediatric Oncology Pharmacist<br>Editor: Dr Amy Mitchell<br>Paediatric Oncology Consultant, |
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| **Consultation document completed: see Appendix A** | |
| **Total number of pages:** | **8** |
| **Is this document to be published in any other format?** | **Yes available on Paediatric Oncology Extranet,** |
| **Does this document replace or revise an existing document?**<br>If so please identify here which document/s<br>**Paediatric Oncology Supportive Care Guidelines S Bevin Version 1,** | |

Paediatric Innovation & Improvement Network

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### 1.2 Scope

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### 1.3 Purpose

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## 2 Implementation

Network updated at Network meeting of changes in guideline.

## 3 Process for Monitoring Effectiveness

Reduced variation in practice has been shown to improve outcomes. Please detail how the impact of this guideline will be measured to demonstrate it's effectiveness and identify areas for further development. Where possible this should include patient reported outcomes.

## 4 References: London supportive care guidelines

## 5 Appendices

Appendix A Paediatric Regional Guideline Consultation Documentation:

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**Appendix A**

**Paediatric Regional Guideline Consultation Documentation**
**Paediatric Oncology Consultants (UHS):**

The Wessex paediatric oncology network have agreed that new guidelines being developed by the wessex paediatric oncology supportive care guidelines working party can be ratified as follows:

All documents are edited by Dr Amy Mitchell and all are approved by at least 1 other Paediatric Oncology Consultant. Any controversial issues are brought before the MDT and final sign off is by the Network Lead Dr Juliet Gray.

On this basis the region accept the use of these guidelines for the management of their shared care paediatric oncology patients.

| **Name of person consulted* (print)** | **Signature** | **Date Signed** |
|---|---|---|
| Dr Juliet Gray | Dr Juliet Gray | 6/10/17 |
| Dr Jessica Bate | Dr Jessica Bate | Author 31/10/17 |
| Dr Amy Mitchell | Dr Amy Mitchell | 31/10/17 |

* this person agrees they have read the guidelines, consulted with relevant colleagues and members of MDT, managers and patients, young people & their families as appropriate. Any queries raised during consultation and review process should be documented with responses and any changes made to guideline.

$ this can be electronic for ease