Hepatic Veno-occlusive Disease (VOD)

NHS University Hospitals of Leicester NHS Trust

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Introduction and Who this Standard Operating Procedure applies to

This CYPICS network standard operating procedure (SOP) has been developed by clinicians from Nottingham Children's Oncology Unit with consultation across the network including from the Leicester Royal Infirmary and has been ratified by the Leicester Children's Hospital guideline process.

This SOP applies to all children and young people under the age of 19 years who are receiving chemotherapy for malignant disease

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Hepatic Veno-occlusive Disease (VOD)

	Title of Guideline	Diagnosis and management of hepatic veno-occlusive disease (VOD) guideline
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	Directorate & Speciality	Directorate: Family Health – Children Speciality: Paediatric Oncology
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	Date when guideline to be reviewed	10/02/2025
	Guideline Number	ASCT/C/015
	Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis)	This guideline applies to children and young people with malignancy that develop VOD.
	Abstract	This guideline outlines risk factors for VOD, clinical, laboratory and radiological features of VOD, diagnostic criteria and management strategies.
	Key Words	Paediatrics. Children. Malignancy. Cancer. Veno-occlusive disease (VOD). Autologous stem cell transplant. Hepatomegaly. Ascites. Bilirubin. Chemotherapy. Radiotherapy.
	Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues?	
1a	meta analysis of randomised controlled trials	
1b	At least one randomised controlled trial	x
2a	at least one well-designed controlled study without randomisation	
2b	at least one other type of well-designed quasi-experimental study	
3	well –designed non-experimental descriptive studies (ie comparative / correlation and case studies)	
4	expert committee reports or opinions and / or clinical experiences of respected authorities	
5	recommended best practise based on the clinical experience of the guideline developer	
	Consultation Process	Paediatric Consultant Oncologists. Emma Ross, Consultant Paediatric, Teenage and Young Adult Oncologist, UHL. Specialist Paediatric Oncology Pharmacists. Margaret Parr, Lead Nurse. Dani Jones, Clinical Educator. Jo Smallman, Ward Manager, E39.
	Target audience	CYPICS Clinical Team.

Authorised by	Name	Signature	Date
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Quality Manager	Elizabeth Ralling		

	This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.

Document Control

Document Amendment Record

Version	Issue Date	Author	Description
V1	December 2020	Wilne, Manning.	Original document.
V2	February 2023	Wilne	Typo amended. No other changes.

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V2 – two amendments made to grammar. No other changes.

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1. Introduction

1.1 The pathogenesis of veno-occlusive disease (VOD) or hepatic sinusoidal obstructive syndrome (SOS) is complex and not fully understood. VOD is most commonly seen in the post haemopoietic stem cell transplant (HSCT) setting but can occur following certain chemotherapy agents in the absence of a transplant.

1.2 The precipitating event appears to be sinusoidal endothelial cell and hepatocyte injury resulting from the chemo/radiotherapy conditioning regimen. As a result of this, micro-thromboses form in the hepatic venules and sinusoids contributing to obstruction of portal flow, portal hypertension and ascites. Fibrosis of venule walls and sinusoids may occur in some patients and appears to be an important determinant of outcome.

1.3 Mild VOD is self-limiting and generally resolves without treatment. Moderate VOD requires treatment but usually resolves. Severe VOD is associated with multi-organ failure with fulminant hepatic failure, encephalopathy and coma and is often fatal. Overall, the mortality from severe VOD is 80% (Corbacioglu et al. 2018).

2. Purpose and Objectives

2.1 This guideline outlines risk factors for VOD, clinical, laboratory and radiological features of VOD and differential diagnoses to assist in the recognition and diagnosis of VOD in a timely manner.

2.2 Criteria for prophylactic treatment and management strategies for VOD according to severity are provided.

2.3 Prompt identification of VOD and initiation of treatment and/or management strategies will reduce the risk of deterioration and enhance patient comfort.

3. Responsibilities

3.1 All members of the clinical team should be aware of and monitor the patient for signs of VOD.

3.2 Diagnosis and management of VOD will be the responsibility of the paediatric oncology/haematology consultants**.**

4. Procedure

4.1 Risk Factors

(CCLG, 2017; Coppell et al, 2003; Dignan et al, 2013; Sulis et al. 2004; Vogelsang and Dalal, 2002)

- Pre-existing hepatic impairment
- Previous VOD
- Prior Treatment with gemtuzumab ozogamicin or inotuzumab ozogamicin
- Previous abdominal radiotherapy
- Previous HSCT
- Hepatic iron overload
- Underlying diagnosis of primary Haemophagocytic Lymphohistiocytosis (HLH), adrenoleukodystrophy or osteopetrosis
- Conditioning regimens containing busulfan (highest risk), high dose melphalan, cyclophosphamide, total body irradiation (TBI). The risk of VOD is much lower with treosulfan containing regimens
- Hepatotoxic chemotherapy without HSCT including busulfan, cyclophosphamide,dactinomycin, tioguanine, dacarbazine, gemtuzumab ozogamicin or inotuzumab ozogamicin
- Concomitant use during HSCT of Norethisterone, Vancomycin, azole anti-fungal's
- Specific polymorphisms of genes encoding glutathione pathway enzymes and tumour necrosis factor-α.

4.2 Clinical Features

- In the HSCT patient, usually occurs before day +30, but may rarely develop later.
- In non-HSCT patients usually occurs 8-15 days post chemotherapy or radiotherapy but can occur later
- Rapid weight gain
- Right upper quadrant pain/tender hepatomegaly
- Ascites

4.3 Laboratory Features

- Rising conjugated bilirubin
- Renal impairment
- Platelet refractoriness

4.4 Radiological Features

- Hepatomegaly and ascites on abdominal ultrasound
- Dampening (mild VOD) or reversal (moderate and severe VOD) of portal venous flow on ultrasound scan. The degree of restriction of flow in the para-umbilical vein may give an indication of severity
- Hepatic venous pressure gradient of greater than 10mmHg above the normal range

4.5 Diagnostic Criteria and Severity

The clinical diagnosis of VOD by the modified Seattle Criteria mandates the presence of 2 or more of the following;

1. Rising bilirubin (>34.2)
2. Hepatomegaly or right upper quadrant pain
3. Ascites +/- unexplained weight gain >2% since transplant

Obtaining a definitive diagnosis of VOD by liver biopsy and measurement of the hepatic venous pressure gradient is usually hazardous in the post-transplant setting and the diagnosis of VOD is generally made using clinical criteria and ultrasound Doppler (Dignan et al. 2013).

Table 1: Corbacioglu *et al* (2018)

EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
LFT[b] (ALT, AST, GLDH)	⩽2 × normal	>2 and ⩽5 × normal		>5
Persistent RT[b]	<3 days	3–7 days		>7 days
Bilirubin (mg/dL)[b, c]		<2		⩾2
Bilirubin (μmol/L)		<34		⩾34
Ascites[b]	Minimal	Moderate	Necessity for paracentesis (external drainage)	
Bilirubin kinetics				Doubling within 48 h
Coagulation	Normal	Normal	Impaired coagulation	Impaired coagulation with need for replacement of coagulation factors
Renal function GFR (mL/min)	89–60	59–30	29–15	<15 (renal failure)
Pulmonary function (oxygen requirement)	<2 L/min	>2 L/min	Invasive pulmonary ventilation (including CPAP)	
CNS	Normal	Normal	Normal	New onset cognitive impairment

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; CNS=central nervous system; CPAP=continuous positive airway pressure; CTCAE=Common Terminology Criteria for Adverse Events; GFR=glomerular filtration rate; GLDH=glutamate dehydrogenase; LFT=liver function test; MOD/MOF=multi-organ dysfunction/multi-organ failure; RT=refractory thrombocytopenia; SOS/VOD, sinusoidal obstruction syndrome/veno-occlusive disease.

[a]If patient fulfills criteria in different categories they must be classified in the most severe category. In addition, the kinetics of the evolution of cumulative symptoms within 48 h predicts severe disease.
[b]Presence of ⩾2 of these criteria qualifies for an upgrade to CTCAE level 4 (very severe SOS/VOD).
[c]Excluding pre-existent hyperbilirubinemia due to primary disease.

4.6 Differential Diagnosis

Other causes of the clinical features should be considered and excluded. These include;

1. Sepsis
2. Viral infection
3. Drug toxicity
4. Cholestasis due to TPN
5. Haemolysis
6. Congestive cardiac failure
7. Acute graft versus host disease

4.7 Prophylaxis

Action to reduce the risk of VOD should be taken wherever possible. This requires consideration regarding the use of hepatotoxic drugs, as well as those metabolized via cytochrome P450.

All patients at risk of VOD will have this documented within their medical notes on admission to the ward post high dose therapy and auto SCT, and should be given **Ursodeoxycholic acid 5mg/kg BD**. This should begin on the day of admission for transplant (in Sheffield) and continuing until day +90. Ursodeoxycholic acid replaces toxic bile acids and protects hepatocytes from cholestasis.

Prophylactic treatment will be commenced in Sheffield and the prescribed prophylaxis should be continued on admission to NUH.

4.8 Management – General

Mild VOD can usually be managed by withdrawal of the causative agent, careful monitoring of liver function and fluid balance, and platelet support.

Moderate or severe VOD (suspected or confirmed), requires immediate intervention and active management and all cases must be discussed immediately with a consultant.

Fluid balance should be recorded accurately and patients weighed twice daily.

Careful fluid balance to maintain intravascular volume and renal perfusion, whilst avoiding extravascular fluid accumulation, by limiting fluid and sodium input and judicious use of diuretics. Spironolactone should be used as the first line diuretic –frusemide may need to be used in patients not responding to Spironolactone alone (refer to BNFc for dosing).

Short duration renal dose dopamine may be considered if diuretics are ineffective.

Monitor coagulation screen and correct any coagulopathy.

Platelet transfusions should be given to maintain the platelet count > $20x10^9/l$. This may require higher doses and more frequent platelet administration than normally expected (see ASCT/C/018 Transfusion Support for children and young people with malignancy and bone marrow failure.

Appropriate analgesia for right upper quadrant pain (see ASCT/C/013 Haematology Oncology Pain Management guideline)

Monitoring for infection as these patients are at an increased risk of infection.

TPN should be modified to minimize hepatocyte injury and limit sodium load.

Concomitant hepatotoxic and nephrotoxic drugs should be avoided wherever possible.

Critical care input should be sought early for patients with VOD. Haemodialysis and ventilatory support may be necessary for renal and pulmonary failure respectively.

Paracentesis should usually be reserved for situations where ascites is causing significant respiratory compromise.

4.9 Management – Severe

The management of severe VOD should include the measures listed in 4.8 plus the use of Defibrotide (Bulley et al. 2007; Chopra et al. 2000; Dignan et al, 2013; Richardson et al. 2010). Defibrotide is only funded for use in the post HSCT setting. A prior approval form on Blueteq must be completed before a supply can be made and treatment is initiated.

Defibrotide

Defibrotide has fibrinolytic and anti-thrombotic properties with proven efficacy in severe VOD, achieving complete resolution of clinical features in 42% with little or no toxicity (Chopra et al, 2000; Richardson et al. 2010).

Defibrotide should be commenced at a dose of **6.25mg/kg/dose IV QDS (total daily dose of 25mg/kg)** for a minimum of 21 days and until signs and symptoms of severe VOD resolve (EMC, 2020). For administration refer to Paediatric Injectable Medicine Guide (Paediatric Medusa).

Other Approaches

Methylprednisolone can be considered for use in the treatment of VOD but the benefit needs to be weighed against the increased risk of infection.

In patients with life-threatening or severe, irreversible VOD, a transjugular intrahepatic portosystemic shunt procedure or orthoptic liver transplant may be considered (Azoulay et al, 2000). Liaise with Birmingham liver unit.

5. Limitations

5.1 Prophylaxis with low dose unfractionated heparin and treatment with tissue plasminogen activator is not recommended as they may be associated with an increased risk of bleeding.

5.2 Defibrotide is not routinely funded for prophylaxis of VOD. If it is to be used in this setting, funding should be agreed in advance.

5.3 Funding approval via Blueteq must be approved prior to the use of defibrotide to ensure the Trust is reimbursed for its use.

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UHL Education and Training

None

Key Words

Children, CYPICS, Haemopoietic Stem Cell Transplant (HSCT), Haematology, Oncology, Young People

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The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
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Details of Changes made during review: V2 – two amendments made to grammar. No other changes.	