bjh guideline

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

Fiona L. Dignan,[1] Robert F. Wynn,[2] Nedim Hadzic,[3] John Karani,[4] Alberto Quaglia,[5] Antonio Pagliuca,[6] Paul Veys,[7] and Michael N. Potter[8] on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation

[1]Department of Haematology, Central Manchester NHS Foundation Trust, [2]Royal Manchester Children's Hospital, Manchester, [3]Paediatric Liver Service & Institute of Liver Studies, King's College Hospital, [4]Department of Radiology, King's College Hospital, [5]Department of Histopathology, King's College Hospital, [6]Department of Haematological Medicine, King's College Hospital, [7]Department of Bone Marrow Transplantation, Great Ormond Street Hospital, and [8]Section of Haemato-oncology, The Royal Marsden NHS Foundation Trust, London, UK

Summary of Key Recommendations

Diagnosis

- **It is recommended that the diagnosis of veno-occlusive disease (sinusoidal obstruction syndrome) [VOD (SOS)] be based primarily on established clinical criteria (modified Seattle or Baltimore criteria) (1A).**
- **Ultrasound imaging may be helpful in the exclusion of other disorders in patients with suspected VOD (SOS) (1C).**
- **It is recommended that liver biopsy be reserved for patients in whom the diagnosis of VOD (SOS) is unclear and there is a need to exclude other diagnoses (1C).**
- **It is recommended that liver biopsies are undertaken using the transjugular approach in order to reduce the risks associated with the procedure (1C).**
- **It is suggested that the role of plasminogen activator inhibitor 1 levels remains an area for further research but that these levels should not form part of the routine diagnostic work-up for VOD (SOS) at present (2C).**

Risk factors

- **It is recommended that patients are assessed for risk factors for VOD (SOS) and that these risk factors are addressed prior to haematopoietic stem cell transplantation (1A).**

Prophylaxis

- **Defibrotide is recommended at a dose of 6·25 mg/kg intravenously four times daily for the prevention of VOD (SOS) in children undergoing allogeneic stem cell transplantation with the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleucodystrophy or osteopetrosis (1A).**
- **Defibrotide is suggested at a dose of 6·25 mg/kg intravenously four times daily for the prevention of VOD (SOS) in adults undergoing allogeneic stem cell transplantation with the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleucodystrophy or osteopetrosis (2B).**
- **Prostaglandin E1 is not recommended in the prophylaxis of VOD (SOS) due to lack of efficacy and toxicity (1B).**
- **Pentoxifylline is not recommended in the prophylaxis of VOD (SOS) due to lack of efficacy (1A).**
- **Ursodeoxycholic acid is suggested for use in the prophylaxis of VOD (SOS) (2C).**
- **Heparin (unfractionated and low molecular weight) is not suggested for use in the prophylaxis of VOD (SOS) due to the risk of increased toxicity (2B).**
- **Antithrombin is not suggested for the prophylaxis of VOD (SOS) due to lack of efficacy (2B).**

Correspondence: Dr. Fiona L. Dignan, Consultant Haematologist, Department of Clinical Haematology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK
E-mail: fldignan@doctors.org.uk

First published online 17 September 2013
doi: 10.1111/bjh.12558

Treatment

- **Defibrotide is recommended in the treatment of VOD (SOS) in adults and children (1B).**
- **Tissue plasminogen activator is not recommended for use in the treatment of VOD (SOS) due to the associated risk of haemorrhage (1B).**
- **N-acetylcysteine is not routinely recommended for use in the treatment of veno-occlusive disease due to lack of efficacy (1A).**
- **Methylprednisolone may be considered for use in the treatment of veno-occlusive disease with the appropriate caveats of caution regarding infection (2C).**
- **Judicious clinical care, particularly in the management of fluid balance, is recommended in the management of VOD (SOS) (1C).**
- **Early discussion with critical care specialists and a specialist hepatology unit is recommended in the management of VOD (SOS) and other treatment options including transjugular intrahepatic portosystemic shunt or hepatic transplantation may be considered (1C).**

Summary

A joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMT) has reviewed the available literature and made recommendations for the diagnosis and management of veno-occlusive disease of the liver following haematopoietic stem cell transplantation (HSCT). This guideline includes recommendations for both prophylaxis and treatment of the condition and includes recommendations for children and adults undergoing HSCT.

Keywords: veno-occlusive disease, prophylaxis, transplant, defibrotide, sinusoidal obstruction syndrome.

Introduction

Veno-occlusive disease of the liver (VOD) occurs as a result of the conditioning treatment administered prior to haemopoietic stem cell transplantation (HSCT). The condition is also known as sinusoidal obstruction syndrome (SOS) in view of the associated characteristic histopathological findings (DeLeve *et al*, 1999). The terms veno-occlusive disease and sinusoidal obstruction syndrome are used interchangeably in this document and the initials VOD are used as the abbreviation for the condition, with the term VOD/SOS preferred by some authors. The mean prevalence of VOD is in the range of 14% (range 0–60%) depending upon the risk factors present (Coppell *et al*, 2010). The condition causes considerable morbidity and mortality and severe VOD is associated with a mortality of over 90% by day +100 following HSCT (McDonald *et al*, 1993; Carreras *et al*, 1998). A number of agents, including defibrotide, have recently been developed and investigated for use in both prophylaxis and treatment of the condition. Despite these developments, there is no uniform consensus on the optimal strategy for managing VOD.

A joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMT) has reviewed the available literature and made recommendations for the diagnosis, prevention and management of VOD in both adults and children. This guideline will discuss VOD following autologous and allogeneic transplant but VOD following solid-organ transplantation or chemotherapy is beyond the scope of this manuscript and will not be discussed. Children are particularly at risk of VOD and any variation between recommendations for adult and paediatric patients will be highlighted in this guideline.

The key areas covered in this guideline are listed below:

- Diagnosis
- Prevention
- Treatment

Methodology

The production of these guidelines involved the following steps:

- Establishment of a working group comprising experts in the field of allogeneic transplantation followed by literature review to 15 February 2013. Medline was searched systematically for publications in English using the following key words: veno-occlusive disease and sinusoidal obstruction syndrome. The reports of major conferences were also reviewed using the same keywords.
- Development of key recommendations based on randomized, controlled trial evidence. Due to the paucity of randomized studies some recommendations are based on literature review and a consensus of expert opinion.
- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified in the BCSH guideline pack and the GRADE working group website. See Appendix 1. Further information is available from the following websites:
  - http://www.bcshguidelines.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html (accessed 28/6/2013)
  - http://www.gradeworkinggroup.org/index.htm (accessed 28/6/2013)
- Review by the BCSH committees, BSBMT executive committee, and the UK Paediatric Bone Marrow Transplant Group.

- Review by sounding board of the British Society for Haematology (BSH) and transplant centres in the UK.

Diagnosis

Clinical diagnostic criteria

The diagnosis of VOD is primarily based on achievement of established clinical criteria including both the Seattle and the Baltimore criteria (McDonald *et al*, 1984, 1993; Jones *et al*, 1987). The original Seattle criteria have been modified to include bilirubin level and percentage of weight gained (Shulman & Hinterberger, 1992). Some studies have also modified these further to use a threshold of 5% weight gain rather than 2% (Corbacioglu *et al*, 2012). These criteria are outlined in Table I. VOD usually occurs within 3 weeks of transplantation although the condition has been reported to occur after this time period (Lee *et al*, 1999). Patients undergoing allogeneic transplant should have a weight measurement recorded daily, be examined daily for signs of fluid overload, ascites and hepatomegaly and have accurate fluid balance recorded. Liver function tests, including alkaline phosphatase, alanine aminotransferase, bilirubin and gamma glutamyl transpeptidase, should be measured daily. Patients undergoing autologous transplantation should also have daily assessment of fluid balance and liver function tests checked several times per week.

Grading of severity

Clinical criteria are also used to define the severity of VOD but these criteria can only be assigned retrospectively. Patients who meet the criteria for VOD but do not require treatment are considered to have had mild VOD. Patients that die from VOD or have an illness that persists beyond 100 d post-transplant are considered to have had severe VOD. Bearman related the risk of developing severe VOD to the degree of weight gain and rise in bilirubin and to the day of transplant when these changes occurred (Bearman *et al*, 1993a; Bearman, 1995). The details of this analysis might not be relevant in the current era because there was no prophylaxis, only patients with defined preparative regimens were included and some current specific and supportive therapies of VOD were not available. However, the findings that the likelihood of severe VOD is increased if weight gain and jaundice occur early after transplant or if the degree of weight gain or rise in bilirubin is marked are likely to be true today.

Patients with VOD frequently develop dysfunction in one or more organ systems. McDonald *et al* (1993) showed that the majority of patients with severe VOD also developed respiratory, cardiac or renal failure more frequently than those with mild or moderate disease. Multi-organ failure can therefore be used as a marker of the severity of the condition.

Table I. Clinical criteria for veno-occlusive disease.

Modified seattle criteria (Shulman & Hinterberger, 1992)	Baltimore criteria (Jones *et al*, 1987)
Two of the following criteria must be present within 20 d of transplant:	Bilirubin must be >34·2 μmol/l (2 mg/dl) within 21 d of transplant and two of the following criteria must be present:
Bilirubin >34·2 μmol/l (2 mg/dl)	Hepatomegaly
Hepatomegaly or right upper quadrant pain	Ascites
Weight gain (>2% from pre-transplant weight)	Weight gain (>5% from pre-transplant weight)

Risk factors

Several risk factors have been identified for the development of VOD. One of the main risk factors is pre-existing hepatic disease. This hepatic dysfunction may result from previous treatment including abdominal irradiation or use of gemtuzumab ozogamicin (Carreras *et al*, 1998; Wadleigh *et al*, 2003). Other causes of pre-existing hepatic disease, including viral hepatitis or iron overload in patients with β thalassaemia major, may also contribute to hepatic toxicity (McDonald *et al*, 1993; Carreras *et al*, 1998).

Stem cell source and choice of conditioning regimen also influence the risk of VOD. The risk of VOD is higher after allogeneic transplantation than after autologous transplantation and is also higher in patients who are receiving a second transplant (McDonald *et al*, 1993). The risk is reduced in patients receiving reduced-intensity conditioning regimens (Hogan *et al*, 2004). Busulfan, particularly in combination with cyclophosphamide has been associated with a higher incidence of VOD (Carreras *et al*, 1998; Cesaro *et al*, 2005). Other drugs, including the use of norethisterone may also be associated with an increased risk of VOD (Hägglund *et al*, 1998).

Underlying diagnosis and age also influence risk. Lower age has been associated with an increased risk of the condition. Cesaro *et al* (2005) reported that, in a multivariate analysis of paediatric patients, age <6·7 years was a significant risk factor for VOD. An increased risk of VOD has also been associated with an underlying diagnosis of osteopetrosis, primary haemophagocytic lymphocytosis or adrenoleucodystrophy (Corbacioglu *et al*, 2006; Ouachée-Chardin *et al*, 2006).

Diagnostic techniques

The differential diagnosis of deranged hepatic function tests following HSCT is wide and includes graft-versus-host disease (GvHD), infection and drug toxicity. The main role of diagnostic techniques including histopathology and imaging

investigations is to exclude other diagnoses as the diagnosis of VOD can primarily be based on clinical criteria.

Histopathology. Veno-occlusive disease was first described following administration of Senecio tea containing pyrrolizidine alkaloid (Willmot & Robertson, 1920). This term was used due to the associated occlusion of the small hepatic veins. More recent work has suggested that the primary change involves the hepatic sinusoids and the term sinusoidal obstruction syndrome (SOS) has also been used to describe this condition (DeLeve *et al*, 2002). A rat model has been described using pyrrolizidine alkaloid (monocrotaline) to demonstrate these histopathological changes. This model showed that the earliest changes occurred in the hepatic sinusoids with loss of endothelial cell fenestrations. Red cell extravasation subsequently occurred through gaps in the sinusoidal lining into the space of Disse. This process resulted in extensive sinusoidal cell injury leading to denudation of the sinusoidal lining and later centrilobular coagulative necrosis, small hepatic vein injury and fibrosis (DeLeve *et al*, 1999).

In an early study on liver tissue obtained at post mortem examination of bone marrow transplant recipients who developed VOD, the early injury was characterized by endothelial damage to sinusoidal and small hepatic vein endothelium, and the identification of small hepatic vein periadventitial factor VIII, and transmural, hepatocytic and sinusoidal fibrin, but no thrombi. Haemorrhagic hepatocellular necrosis was also described. Late injury consisted of fibrous obliteration of small hepatic veins (Shulman *et al*, 1987). In a later study, the same group showed that the severity of clinical VOD correlated with the number of histological changes in the acinar zone 3. In particular, eccentric luminal narrowing and phlebosclerosis of small hepatic veins, sinusoidal fibrosis and hepatocyte necrosis were associated with severe VOD (Shulman *et al*, 1994). Other histological features include nodular regenerative hyperplasia and cholestasis. The distribution of the histological changes can be patchy and sampling error may be a limiting factor (DeLeve *et al*, 2009). In particular, injury to the small hepatic vein may not be represented in a biopsy specimen. Thrombosis of the large hepatic vein or right cardiac failure can result in secondary small hepatic vein and sinusoidal involvement that is indistinguishable histologically from VOD. Liver histology has a role in differentiating between VOD and other causes of liver dysfunction in HSCT patients, including drug or sepsis-induced cholestasis, viral infections, and GvHD.

Hepatic biopsy can be challenging following allogeneic transplant due to high bleeding risk secondary to thrombocytopenia. Some studies have used transjugular hepatic biopsies to try and reduce this risk. Carreras *et al* (1993) undertook transjugular hepatic biopsies on 82 patients and had reported no serious complications. Shulman *et al* (1995) undertook a comparative study of two different instruments for undertaking hepatic biopsies in 60 patients. Both studies showed that a hepatic venous pressure gradient of >10 mm Hg correlated with a histological diagnosis of VOD. Neither report showed a significant proportion of patients meeting histological criteria who did not meet clinical criteria (Carreras *et al*, 1993; Shulman *et al*, 1995). Hepatic biopsies using the transjugular approach may be helpful where the diagnosis is not clear but are not required in patients who meet the clinical criteria for VOD.

Imaging. Several studies have focused on the role of ultrasound in the diagnosis of VOD. Most of these studies have used non-specific markers and it is suggested that the main role of ultrasound is to exclude the presence of other diagnoses. Reported abnormalities have included thickening of the gallbladder wall, reversal of portal vein blood flow, ascites, hepatomegaly and splenomegaly (Brown *et al*, 1990; Herbetko *et al*, 1992; Hommeyer *et al*, 1992; Benya *et al*, 1993; Teefey *et al*, 1995; Lassau *et al*, 1997; Hashiguchi *et al*, 2005). Although several prospective studies have been undertaken, these investigations have failed to show consistent results (reviewed in Mahgerefteh *et al*, 2011).

Lassau *et al* (1997) undertook a prospective study of 100 patients. This study included pre-transplant ultrasound scans and weekly ultrasound scans during the transplant admission. Patients were given three scores: gray-scale score, Doppler score and total score and these were found to correlate with the clinical diagnosis of VOD (Lassau *et al*, 1997). This study also identified a significant difference in scores between patients with VOD and those with hepatic GvHD. Herbetko *et al* (1992) undertook a prospective study of 65 patients undergoing bone marrow transplantation (BMT). Gray-scale and Doppler assessments were undertaken at baseline and in the third week after transplantation. No gray-scale abnormalities were identified in the VOD group and only one patient had an abnormality in portal vein velocity (Herbetko *et al*, 1992). A second prospective study of 21 patients from Seattle also failed to show any gray-scale abnormalities to be associated with VOD (Hommeyer *et al*, 1992). A more recent study (McCarville *et al*, 2001) prospectively reviewed 202 serial sonograms from 48 patients. Ultrasound parameters included hepatic artery resistive index, direction and velocity of portal venous flow and thickness of gall bladder wall, but the study failed to show any benefit over clinical criteria in the diagnosis of VOD (McCarville *et al*, 2001).

Fewer studies have been undertaken to investigate the role of other imaging modalities. A small single-centre retrospective study of 18 patients reported that the presence of periportal oedema, ascites and a narrow right hepatic vein on computerized tomography scans may favour a diagnosis of VOD over hepatic GvHD (Erturk *et al*, 2006). There are a few case reports detailing the findings of magnetic resonance imaging scans in patients with VOD (van den Bosch & van Hoe, 2000; Mortelé *et al*, 2002; Dumont *et al*, 2004). Features included patchy signal enhancement of the liver, hepatomegaly, ascites, hepatic vein narrowing, peri-portal cuffing and gallbladder wall thickening or hyperintensity. A more

recent study reported that gadotexic acid-enhanced magnetic resonance imaging was highly specific in the diagnosis of VOD in a series of patients with chemotherapy-treated colorectal liver metastases (Shin *et al*, 2012).

Plasminogen activator inhibitor-1 levels. Several studies have investigated the role of plasma levels of plasminogen activator inhibitor-1 (PAI-1) as a diagnostic marker in VOD. Salat *et al* (1997) measured PAI-1 levels in 31 post-transplant patients who developed hyperbilirubinaemia >51·3 μmol/l. PAI-1 was significantly elevated in patients with VOD compared to those patients with GvHD or other hepatic damage (Salat *et al*, 1997). Lee *et al* (2002) measured haemostatic parameters at five time points post-transplant in 115 patients (50 of whom developed VOD) and identified PAI-1 as a diagnostic marker and a predictor of severity of VOD. Other studies have reported similar results (Kaleelrahman *et al*, 2003; Pihusch *et al*, 2005; Sartori *et al*, 2012). A decrease in PAI-1 levels has also been shown to correlate with treatment outcome (Richardson *et al*, 2010). The measurement of PAI-1 levels is an area of ongoing research but currently the practicalities of undertaking the test preclude its routine use in the UK.

Prevention of VOD

VOD and the preparative regimen

For an individual patient, the likelihood of VOD will depend on the interaction of their own risk factors and the transplant preparative regimen. Recognition of this potential interaction before the transplant will enable the risk of VOD in that patient to be reduced before the question of pharmacological prophylaxis is even considered. Reversible patient risk factors should be addressed, e.g. reducing iron overload in thalassaemic patients. Patients with irreversible risk factors might be better managed with a reduced intensity conditioning protocol. VOD is less common in patients receiving a treosulfan rather than a busulfan conditioning regimen and use of this drug has consequently increased significantly, particularly in paediatric practice (Slatter *et al*, 2011). For those patients receiving a busulfan protocol, busulfan pharmacokinetic monitoring will allow individualized targeting of busulfan to a regimen-specific therapeutic window thereby ensuring both transplant efficacy and reduced VOD toxicity. A recent prospective study reported recently in abstract form has shown that the incidence of VOD is reasonably low at 5% following IV busulfan (n = 1025) (Bredeson *et al*, 2013). The incidence of VOD following total body irradiation (TBI)-based regimens in the same study was 1% (n = 458) (Bredeson *et al*, 2013). The busulfan target pharmacokinetic might be adjusted where the conditioning regimen includes melphalan or other agents that might add to VOD risk (Bartelink *et al*, 2012). The addition of cyclophosphamide to busulfan has been associated with a higher incidence of VOD (Carreras *et al*, 1998; Cesaro *et al*, 2005), and many investigators have now replaced cyclophosphamide with fludarabine, particularly in children undergoing HSCT for genetic diseases; further data is required to determine if this combination significantly reduces the risk of VOD in this patient population.

Defibrotide

Defibrotide is a single-stranded polydeoxyribonucleotide that has anti-thrombotic, anti-inflammatory and anti-ischaemic properties. This agent appears to have a protective effect against endothelial cell injury and has not been associated with an increased bleeding risk despite reducing procoagulant activity, increasing fibrinolysis and modulating platelet activity (Berti *et al*, 1990; Ulutin, 1993; Coccheri *et al*, 1988; Falanga *et al*, 2003; Echart *et al*, 2009). Following reports of the success of defibrotide in the treatment of VOD, several studies have focused on the role of this agent in prophylaxis. Defibrotide is an unlicensed drug and clinicians using this agent should be aware that its use does not have approval of the regulatory authorities. The role of this agent is discussed in these guidelines for prophylaxis and treatment of VOD as there are no similar licensed agents available.

Several retrospective series have been published. Chalandon *et al* (2004) reported on 52 patients (median age 36·5 years, range 5–60) who received defibrotide at a dose of 10–25 mg/kg/d from the day prior to conditioning until day +20 following transplant. In addition, patients received a continuous infusion of intravenous heparin. The diagnosis of VOD was based on the Baltimore criteria and results were compared with an historical control group who received heparin alone (Chalandon *et al*, 2004). There were no cases of VOD in the treatment group compared to 10/52 in the control group (P = 0·001). All patients underwent allogeneic transplantation and the majority (45/52) of the treatment group had undergone myeloablative conditioning. The event-free survival was also higher in the treatment group (P = 0·02).

Dignan *et al* (2007) reported a retrospective series of 58 adult patients who received defibrotide at a dose of 5 mg/kg intravenously twice daily from day +1 until day +21 following allogeneic transplantation without the concurrent use of heparin. No patients met the Baltimore criteria for VOD although it should be noted that 37/58 patients received reduced-intensity conditioning regimens and may have been at lower risk of developing the condition (Dignan *et al*, 2007). There were no significant haemorrhagic events.

Encouraging data also exist from small studies in high-risk groups. Cappelli *et al* (2009) reported on a series of 63 allogeneic transplants undertaken in children with β-thalassaemia and additional risk factors for developing VOD including liver fibrosis, iron overload, hepatitis C viral infections, busulfan-based conditioning regimens or receipt of methotrexate and ciclosporin as GvHD prophylaxis. Defibrotide was administered orally (40 mg/kg/d) from median of day −9 to median day +29. One patient met the Seattle criteria for VOD but had actually stopped defibrotide

prophylaxis 6 d prior to diagnosis due to a high risk of haemorrhage (Cappelli *et al*, 2009). Corbacioglu *et al* (2006) reported a series of 9 children with osteopetrosis who received a median dose of 40 mg/kg/d intravenously of defibrotide. Only one patient met the Seattle criteria for VOD compared to 7/11 (63·6%) of patients in an historical control group (Corbacioglu *et al*, 2006). Promising results have also been reported in 5 patients who had received gemtuzumab ozogamicin prior to transplant (Versluys *et al*, 2004).

The results of a phase 3 open-label randomized controlled trial have recently been reported (Corbacioglu *et al*, 2012). This multicentre study included 356 children who had undergone autologous (108 children) or allogeneic transplantation with myeloablative conditioning. Patients had one or more risk factors for VOD including pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan and melphalan, prior treatment with gemtuzumab ozogamicin or a diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleucodystropy or osteopetrosis. The primary endpoint was incidence of VOD by day +30 as defined by the modified Seattle criteria. Patients in the treatment group received 6·25 mg/kg of defibrotide intravenously four times daily from the start of conditioning until day +30 or discharge. Patients were permitted to receive ursodeoxycholic acid. Heparin was only permitted in patients with central venous catheters to maintain patency of the catheter. Twenty-two (12%) patients in the treatment arm developed VOD compared to 35 (20%) in the control arm (Z test for competing risk analysis $P = 0{\cdot}0488$; log rank test $P = 0{\cdot}0507$). The cumulative incidence of non-relapse mortality at 180 d was 9% in both groups. This result might be attributable to the fact that the study was not designed to show differences in mortality and that the protocol permitted patients in the control group to receive defibrotide treatment if they developed VOD. There was a significant difference in the proportion of patients with VOD- associated renal failure (2/180 patients in the defibrotide group compared to 10/176 patients in the control group, $P = 0{\cdot}0169$). In the allogeneic transplant groups, the incidence of grade I-IV acute GvHD was lower in treatment group at day 30 and day 100 ($P = 0{\cdot}0057$ and $P = 0{\cdot}0046$, respectively). There was no significant difference in the risk of haemorrhagic events between the two groups.

There is no pharmacological or physiological reason why defibrotide prophylaxis would not also reduce the risk of VOD in adults undergoing HSCT. At present, we do not know the optimal dose or duration of prophylaxis and whether the intravenous route is superior to the oral route of administration. In addition, we do not know that prophylaxis with defibrotide is superior to early treatment but the mortality from established VOD is sufficiently high to justify prophylaxis in high-risk patients. In the absence of any data regarding the duration of prophylaxis, it may be reasonable to continue defibrotide prophylaxis until day +14 or until engraftment has occurred. The use of defibrotide in this setting would be at the discretion of the treating physician as it is an unlicensed drug and, at present, the data available primarily relates to its use in children. Further work in this area could reasonably include a dose-finding study and a trial of prophylactic defibrotide in adults. The above data suggest that defibrotide can be used safely without an increased risk of haemorrhage and its use is therefore recommended at a dose of 6·25 mg/kg intravenously four times daily in the prevention of VOD (SOS) in adults and children undergoing allogeneic stem cell transplantation with the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan containing regimens, prior treatment with gemtuzumab ozogamicin or diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleucodystrophy or osteopetrosis. The use of defibrotide would primarily be used in patients undergoing myeloablative conditioning but may be considered in high-risk patients receiving reduced intensity regimens at the discretion of the treating physician. Defibrotide may also be helpful in the prophylaxis of patients undergoing autologous transplantation using high-risk conditioning regimens, e.g. busulfan and melphalan.

Prostaglandin E1

There are a few early reports of the use of prostaglandin E1 in the prevention of VOD. Gluckman *et al* (1990) used prostaglandin E1 as a continuous infusion from day−8 until day 30 after allogeneic transplant at a dose of 0·3 μg/kg/h. A treatment group of 50 patients were compared to a control group of 59 patients. The actuarial incidence of VOD was 12·2% in the treatment group compared to 25·5% in the control group ($P = 0{\cdot}05$) (Gluckman *et al*, 1990). A phase I/II study used prostaglandin E1 at 4 dose levels in 24 patients at high risk of VOD (Bearman *et al*, 1993b). Prostaglandin E1 was stopped in 50% of the patients due to severe toxicities, including cutaneous erythema and desquamation, fluid retention and oedema, severe pain in dependent extremities and hypotension (Bearman *et al*, 1993b). Severe side effects have also been reported by other groups (Bordigoni *et al*, 1991). More recently, a retrospective study used prostaglandin E1 (40 patients) or low-dose heparin (10 patients) in 50 paediatric patients according to physician preference. This group was compared to 35 patients who did not receive prophylaxis. There was no difference in the incidence of VOD although no patients in the treatment group developed severe VOD (Song *et al*, 2006).

Pentoxifylline

Pentoxifylline, a xanthine derivative that has been shown to downregulate tumour necrosis factor (TNF)-alpha production *in vitro*, has been used in the prophylaxis of regimen-related toxicities following stem cell transplant including VOD. Attal

et al (1993) undertook a prospective randomized controlled trial of 140 patients and failed to show a benefit in the treatment arm (Attal *et al*, 1993). These results were replicated in a similar trial by the Seattle group (Clift *et al*, 1993). Ferrà *et al* (1997) used pentoxifylline, ciprofloxacin and prednisolone in combination but did not show any reduction in VOD risk and this combination was associated with a higher risk of infectious complications.

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid that can result in the reduction of hydrophobic bile acids, which can be toxic to hepatic parenchymal cells. A number of studies have attempted to evaluate the role of ursodeoxycholic acid in the prophylaxis of VOD and of other hepatic complications of allogeneic transplantation including GvHD. Essell *et al* (1998) undertook a randomized, double-blind, placebo-controlled single centre study using UDCA 300 mg twice daily (or 300 mg in the morning and 600 mg in the evening if the patients body weight was >90 kg). Sixty-seven patients were included who had received bone marrow from a related donor and a conditioning regimen including busulfan plus cyclophosphamide. The study drug was started prior to administration of conditioning and continued until 80 d after transplantation. VOD was diagnosed if at least two of the following conditions were present <30 d from transplant: bilirubin level >51·31 μmol/l, painful hepatomegaly and fluid accumulation as defined by ascites or >5% weight gain. The incidence of VOD was significantly less in the UDCA group (15% compared to 40%, $P = 0{\cdot}03$). The difference in the survival rates between the two groups at 100 d was not significant (77% in UDCA group compared to 59% in placebo group, $P = 0{\cdot}19$) (Essell *et al*, 1998).

Ohashi *et al* (2000) undertook a prospective, randomized, open-label multicentre study to evaluate the role of UDCA 600 mg daily from day−21 to day +80 after transplantation compared to placebo in 132 patients. VOD was diagnosed in the presence of two of the following criteria: bilirubin ≥34·2 μmol/l, painful hepatomegaly and fluid accumulation due to ascites or >2% increase in body weight. Patients received a variety of conditioning regimens and this study included a small number of patients undergoing autologous transplantation. Fourteen (10·6%) of the 132 patients developed VOD. The incidence of VOD was significantly lower in the UDCA arm (3% compared to 18·5%, $P = 0{\cdot}004$). The incidence of GvHD and relapse were similar in both groups. At 24 weeks after transplantation, there were 15 deaths in the UDCA arm and 16 deaths in the control arm (Ohashi *et al*, 2000). There were no adverse events attributable to UDCA.

These results have not been confirmed by all studies. Ruutu *et al* (2002) undertook a prospective randomized open-label multicentre trial of 242 patients. The study group ($n = 123$) were allocated to receive 12 mg/kg/d of UDCA from day−1 until day +90 following transplantation. This study showed that there was no significant difference in the incidence of VOD but that there was a significantly lower incidence of grade III or IV acute hepatic GvHD ($P = 0{\cdot}01$) and that survival at 1 year was significantly better in the UDCA group (71% vs. 55%, $P = 0{\cdot}02$) (Ruutu *et al*, 2002). Park *et al* (2002) undertook a randomized trial comparing UDCA and heparin to heparin alone in patients undergoing autologous or allogeneic transplantation. There was no significant difference in the incidence of VOD (15·9% vs. 19·3%, $P = 0{\cdot}348$) or in survival at 100 d post transplant (Park *et al*, 2002).

A systematic review pooled the results of the above three randomized studies comparing UDCA to no treatment and demonstrated a reduced risk of VOD in patients receiving UDCA (relative risk, 0·34; 95% confidence interval 0·17–0·66) (Tay *et al*, 2007). UDCA is suggested for prophylaxis of VOD. The use of defibrotide in combination with UDCA in patients at high risk of developing VOD may be considered at the discretion of the treating physician.

Heparin

Both unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have been studied in the prophylaxis of VOD. Attal *et al* (1992) reported a prospective randomized trial of low dose UFH (100 units/kg/d administered by continuous intravenous infusion from day−8 until day +30 or day of discharge). VOD was diagnosed clinically with histological confirmation if another identifiable cause of hepatic disease was present. Patients underwent allogeneic and autologous transplantation with a variety of conditioning regimens. Overall, 2/81 (2·5%) in the heparin group developed VOD and 11/80 (13·7%) in the control group developed VOD ($P < 0{\cdot}01$). In the allogeneic transplant group, the incidence of VOD was less in patients who had received heparin (0% vs. 7%, $P < 0{\cdot}01$). There were three minor bleeding events in the heparin arm. There was no significant difference in survival at 100 d following transplant between the two arms (Attal *et al*, 1992). A phase II study in 50 children used UFH at a dose of 100 units/kg/d by continuous infusion and showed a significant reduction in diagnoses of VOD (defined by modified Seattle criteria) when compared to an historical control group (10% vs. 25·7%, $P < 0{\cdot}05$) (Rosenthal *et al*, 1996).

These results have not been replicated in all studies. An earlier study of patients undergoing autologous transplantation (98 enrolled as part of a randomized controlled trial and 136 enrolled as part of a cohort study) used 1 mg/kg daily of intravenous heparin from day of transplant until engraftment achieved (Marsa-Vila *et al*, 1991). This study did not show a reduced incidence of VOD. In the randomized trial, 2·2% of patients in the control arm developed VOD compared to 7·7% in the heparin arm (Marsa-Vila *et al*, 1991). There was no increase in adverse events in the heparin arm. Reiss *et al* (2002) also reported no benefit of

UFH in a retrospective study of 241 of children and young adults undergoing allogeneic or autologous transplantation.

LMWH has been investigated in several series including one randomized controlled trial (Or *et al*, 1996). This study included 61 patients undergoing transplantation (allogeneic = 24, autologous = 37) who were randomized to receive 40 mg of enoxaparin once daily or placebo prior to BMT conditioning until day +40 or discharge. The incidence of hepatomegaly and the duration of elevated bilirubin were less in the treatment arm ($P = 0{\cdot}04$ and $P = 0{\cdot}01$, respectively). There was no increase in haemorrhagic events in the treatment arm (Or *et al*, 1996). A prospective phase II study investigated the safety and feasibility of using dalteparin 2500 international units once daily subcutaneously in 40 patients (Forrest *et al*, 2003). There were 3 clinically significant bleeding episodes and 24 patients developed minor bleeding that did not require specific therapy. Simon *et al* (2001) undertook a retrospective cohort study of 462 adult patients who had undergone autologous or allogeneic stem cell transplant. Patients who had received heparin, heparin and prostaglandin E1 or LMWH (enoxaparin 30 mg twice daily) were compared to an historical control group who received no prophylaxis (Simon *et al*, 2001). VOD was diagnosed using Seattle criteria. VOD was diagnosed in 22% of the no prophylaxis group, 11% of the heparin group, 12% of the heparin and prostaglandin E1 group and 4% of the LMWH group ($P = 0{\cdot}0002$). Fatal haemorrhages occurred in 4 patients in the control group, 1 in LMWH group and 3 in the heparin group.

A systematic review and meta-analysis which included 12 studies using LMWH or UFH as prophylaxis for VOD (2782 patients) reported that anticoagulation did not significantly reduce the risk of VOD (pooled relative risk, 0·90; 95% confidence interval, 0·62–1·29) (Imran *et al*, 2006).

Anti-thrombin

Anti-thrombin has been investigated in a number of small studies as levels of anti-thrombin are low in patients with VOD and anti-thrombin has a protective effect on the vascular endothelium (Morris *et al*, 1997; Mertens *et al*, 1999). Peres *et al* (2008) reported a retrospective review of 48 patients with VOD who received early treatment with anti-thrombin. The overall 100-d mortality was 17% (10% in the mild/moderate group, 39% in the severe group). Haussmann *et al* (2006) undertook a prospective study comparing the use of pre-emptive anti-thrombin in 91 children compared to a historical control group of 71 children who received no prophylaxis. The modified Seattle criteria were used to diagnose VOD. Pre-emptive anti-thrombin was given at a dose of 50–100 units/kg in HSCT patients with plasma anti-thrombin levels of ≤70%. There was no significant difference in the incidence of VOD between the two groups. Fourteen patients in the treatment arm developed VOD and were treated with a combination of defibrotide and anti-thrombin therapy. All of these patients achieved complete remission of VOD as defined by complete resolution of VOD-and multi-organ failure-related symptoms and a bilirubin of <34 μmol/l. Ninety-three percent (13/14) were alive at 100 d following transplantation (Haussmann *et al*, 2006).

Treatment of Veno-occlusive Disease

Defibrotide

Several studies in both adults and children have reported on the efficacy of defibrotide in the treatment of VOD. Richardson *et al* (1998) first reported on 19 patients who had received defibrotide for the management of severe VOD in a compassionate use study. Intravenous defibrotide was administered in doses ranging from 5 mg/kg/d to 60 mg/kg/d. Patients were included if they had a clinical diagnosis of VOD (bilirubin >34·2 μmol/l and two of the following: hepatomegaly and/or right upper quadrant pain, ascites or >5% weight gain above admission weight) or a positive biopsy result. In addition, patients who presented within 16 d of transplant had a predicted risk score of 40% defined by the Bearman model (Bearman *et al*, 1993a) or, if presenting after day +16, VOD constituted their main clinical problem. Eight patients (42%) had resolution of VOD as defined by resolution of bilirubin to <34·2 μmol/l and improvement of other symptoms and signs of VOD.

These encouraging data led to an additional 69 patients receiving defibrotide on an emergency use basis. Patients were enrolled prospectively from 8 transplantation centres and received a dose ranging from 5 to 60 mg/kg/d. Patients were included based on a clinical diagnosis (bilirubin ≥34·2 μmol/l, hepatomegaly and/or right upper quadrant pain, and ≥5% weight gain from admission, with or without ascites) or two clinical criteria and positive hepatic biopsy. Patients had to have a predicted risk score of 30% as defined by the Bearman model (Bearman *et al*, 1993a) or, if presenting after day +16, VOD was considered their main clinical problem and organ failure was present in at least one organ system. Complete response (CR) was defined as in the pilot study. The CR rate in 88 patients (including the 19 patients in the pilot study) was 36% and survival at day +100 was 35% (Richardson *et al*, 2002).

A randomized phase II dose-finding study was subsequently conducted by the same group (Richardson *et al*, 2010). Adult or paediatric patients were included if they had a clinical diagnosis of VOD by day +35 post-HSCT or biopsy proven VOD. Patients were also included if they had portal vein flow reversal on ultrasound, jaundice and one other clinical criterion. Patient eligibility was also defined by the severity criteria from the previous study, specifically multi-organ failure (Richardson *et al*, 2002). Patients were randomized to receive lower dose defibrotide (25 mg/kg/d, $n = 75$) or higher dose defibrotide (40 mg/kg/d, $n = 74$) administered intravenously every 6 h for ≥14 d or until CR, progression of VOD or unacceptable toxicity was observed (Richardson *et al*, 2010). CR was defined

as total serum bilirubin <34·2 μmol/l with resolution of VOD-related multi-organ failure. The overall CR rate was 46% and there was no significant difference between the two arms. The day +100 post-HSCT survival rates were 42% and again there was no significant difference between the two arms. There was a slightly higher rate of adverse events in the higher dose arm (10% vs. 7%) but this difference did not achieve statistical significance.

Given that there was no difference in efficacy or toxicity in the phase II randomized study (Richardson *et al*, 2010), the lower dose of defibrotide was subsequently selected for phase III trials in VOD. The results of a phase III study comparing the use of defibrotide in the treatment of severe VOD to an historical control group have been presented in abstract form and updated recently (Richardson *et al*, 2009). Patients were included if they met the Baltimore criteria for VOD and CR was assessed as bilirubin <34·2 μmol/l and resolution of multi-organ failure. One hundred and two patients received defibrotide intravenously at a dose of 6·25 mg/kg four times daily and were compared to 32 historical control patients. The day +100 CR rate was 24% in the treatment arm compared to 9% in the historical control group ($P = 0{\cdot}013$). The day +100 mortality rate was 62% in the treatment arm compared to 75% in the control group ($P = 0{\cdot}03$). Haemorrhagic adverse events were similar in the two groups (Richardson *et al*, 2009).

Following completion of the above trial, a single arm phase II study was pursued and patients were included if they met the eligibility for the trial or if they had non-severe VOD or had developed VOD after chemotherapy rather than after HSCT. The results of this expanded access programme have been reported in abstract form (Richardson *et al*, 2011, 2012). The latest interim analysis reported on 333 patients (305 who had undergone HSCT with 274 undergoing an allogeneic transplant). Two hundred and twenty patients had severe disease at study entry. The overall CR rate was 30% with a 50% survival rate at day +100 in HSCT patients. In the patients with non-severe VOD the CR rate was 39% and the day +100 survival rate was 65%. The 155 patients who met the original trial criteria had a CR rate of 29% compared to 9% in the historical control group ($P = 0{\cdot}0019$) and superior survival at day +100 (49% vs. 25%, $P = 0{\cdot}0016$). The main toxicities were haemorrhage in 18% and hypotension in 4% of patients with 2% of patients experiencing life-threatening haemorrhage. A low incidence (8%) of all grades of acute GvHD was also noted (Richardson *et al*, 2012).

The role of defibrotide in the treatment of VOD has also been investigated by other groups. Corbacioglu *et al* (2004) reported a retrospective analysis of 45 patients aged between 0·2 and 20 years who received defibrotide intravenously at an average dose of 40 mg/kg/d. VOD was diagnosed using the Baltimore criteria. CR was defined as resolution of VOD and multi-organ failure-related symptoms and a bilirubin of <34·2 μmol/l. Twenty-two patients had severe disease and 23 had moderate or mild disease. The overall CR rate was 76% with a survival rate of 64% at day +100 (Corbacioglu *et al*, 2004). Bulley *et al* (2007) have also reported a retrospective series of the use of defibrotide in paediatric patients. In this series of 14 patients, 60% stopped defibrotide due to clinical improvement and the survival rate to day +100 was 79% (Bulley *et al*, 2007). The European compassionate-use study (Chopra *et al*, 2000) included 40 patients who fulfilled either the Baltimore or Seattle criteria for VOD and received intravenous defibrotide (10 to 40 mg/kg daily). Twenty-two patients (55%) showed a CR as defined by bilirubin <34·2 μmol/l and resolution of signs/symptoms of VOD and end-organ dysfunction. The survival rate at day +100 was 43%. The CR rate in the 10 poor-risk patients was 36% (Chopra *et al*, 2000).

Further work is required to investigate the optimal dose of defibrotide, the optimal route of administration and the optimal dose to use in patients who have received defibrotide as a prophylactic agent. Until future studies address these questions, intravenous defibrotide is recommended in the treatment of adults and children with VOD at a dose of 25 mg/kg/d.

Tissue plasminogen activator (TPA)

Tissue plasminogen activator (TPA) has been used in the treatment of VOD in a number of studies. Many of these reports only included small numbers of patients (Goldberg *et al*, 1996; Hágglund *et al*, 1996). The largest study to date retrospectively reviewed 42 patients who received total doses of TPA ranging from 5·4–120 mg intravenously over 2–4 d with heparin at a bolus dose of 1000 units at the start of recombinant human (rh)-TPA and 150 units/kg/d by infusion for 10 d (Bearman *et al*, 1997). VOD was defined clinically by the presence of two of the following features by day 20 post-transplant: jaundice, painful hepatomegaly or unexplained weight gain. Response was defined as a 50% reduction in total serum bilirubin by 50% within 10 d of starting treatment. The response rate was 29% (12 patients). The survival rate at day +100 was 24% (10 patients). Thirty-seven patients (88%) bled following treatment and 24% had a severe haemorrhage. Severe bleeding was the cause of death in 3 patients and may have contributed to the cause of death in a further three patients.

N-acetylcysteine (NAC)

N-acetylcysteine (NAC) has been used in one retrospective study of 3 patients with severe VOD as defined by the Bearman criteria (Ringdén *et al*, 2000). NAC was administered at a loading dose followed by 50–150 mg/kg/d for 12–31 d and all 3 patients had a CR and were alive at 100 d after transplantation. A prospective randomized study of 160 patients was subsequently undertaken by the same group (Barkholt *et al*, 2008). Patients with a bilirubin >26 μmol/l and/or elevated alanine aminotransferase (84 units/l) were randomized to receive 100 mg/kg/d of NAC or no treatment. Two

patients in the NAC group developed VOD and three patients in the control group developed VOD, showing no significant benefit of NAC in reducing hepatic toxicity post-HSCT (Barkholt *et al*, 2008).

Methylprednisolone

High dose methylprednisolone has also been used in the treatment of VOD. A prospective study of 48 patients with VOD as defined by the Seattle criteria assessed the role of 0·5 mg/kg of methylprednisolone IV bd for 14 doses (Al Beihany *et al*, 2008). Multi-organ failure was present in 31% of patients. Response was defined as a reduction in the total serum bilirubin by 50% or more within 10 d of initiation of corticosteroids. Sixty-three percent of patients responded and 28/48 (58%) were alive at 100 d from transplant. A recent paediatric retrospective study described 9 patients who received methylprednisolone 500 mg/m^2 IV every 12 h for 6 doses (Myers *et al*, 2013). Eight of these patients had multi-organ failure secondary to VOD. Response was defined as a 50% reduction in bilirubin level by 10 d after the commencement of therapy. Six patients responded to treatment. Four patients also received treatment with defibrotide. Overall survival was 78% (Myers *et al*, 2013). Methylprednisolone may be considered for the use in the treatment of VOD with the appropriate caveats of caution regarding infection.

Supportive care

The mainstay of supportive care in patients with VOD is judicious clinical care, particularly in the management of fluid balance. The total amount of fluids should be restricted and diuretic therapy should be administered in severe fluid overload. Renal replacement therapy may be required in severe cases. Patients with multi-organ failure will require management in a high-dependency or intensive care environment. Early discussion with a specialist hepatology unit is advised regarding further therapeutic options.

There have been case reports of successful liver transplantation in occasional patients with VOD but this procedure relies on organ availability and is associated with considerable risks of liver graft rejection and peri-operative multi-organ failure (Schlitt *et al*, 1995). Transjugular intrahepatic portosystemic shunt (TIPS) has been used in several case reports (Alvarez *et al*, 2000; Zenz *et al*, 2001). One study of 10 patients reported that 5 patients died within 10 d of TIPS with no improvement (Azoulay *et al*, 2000). Four patients initially showed some improvement in clinical parameters but subsequently died. One patient showed complete resolution of VOD after 6 months (Azoulay *et al*, 2000).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Committee for Standards in Haematology, the British Society for Blood and Marrow Transplantation nor the publishers accept any legal responsibility for the content of these guidelines.

Acknowledgements

FLD reviewed the literature and wrote the initial draft of the manuscript. MNP chaired the writing group, reviewed the literature, revised the manuscript and represented BCSH. RW represented BSBMT, reviewed the literature and revised the manuscript. AP, PV, AQ, NH, JK reviewed the literature and revised the manuscript. The authors are grateful to the BCSH task force and sounding board, UK Paediatric BMT group, BSBMT executive committee and transplant centres for their support in preparing these guidelines. The authors wish to thank Dr Chloe Anthias for her help in undertaking the initial literature review for these guidelines.

Conflict of interest

FLD, JK, AQ, NH and PV have no conflicts of interest to declare. MNP, RW and AP have participated in an advisory board for Gentium. AP has received speaker's fees from Gentium.

References

Al Beihany, A., Al Omar, H., Sahovic, E., Chaudhri, N., Al Mohareb, F., Al Sharif, F., Al Zahrani, H., Al Shanqeeti, A., Seth, P., Zaidi, S., Morshed, M., Al Anazi, K., Mohamed, G., Gyger, M. & Aljurf, M. (2008) Successful treatment of hepatic veno-occlusive disease after myeloablative allogeneic hematopoietic stem cell transplantation by early administration of a short course of methylprednisolone. *Bone Marrow Transplantation*, **41**, 287–291.

Alvarez, R., Bañares, R., Casariego, J., Echenagusía, A., Simó, G., Alvarez, E., Serrano, D. & Díez-Martín, J.L. (2000) Percutaneous intrahepatic portosystemic shunting in the treatment of veno-occlusive disease of the liver after bone marrow transplantation. *Journal of Gastroenterology and Hepatology*, **23**, 177–180.

Attal, M., Huguet, F., Rubie, H., Huynh, A., Charlet, J.P., Payen, J.L., Voigt, J.J., Brousset, P., Selves, J. & Muller, C. (1992) Prevention of hepatic veno-occlusive disease after bone marrow transplantation by continuous infusion of low-dose heparin: a prospective, randomized trial. *Blood*, **79**, 2834–2840.

Attal, M., Huguet, F., Rubie, H., Charlet, J.P., Schlaifer, D., Huynh, A., Laurent, G. & Pris, J. (1993) Prevention of regimen-related toxicities after bone marrow transplantation by pentoxifylline: a prospective, randomized trial. *Blood*, **82**, 732–736.

Azoulay, D., Castaing, D., Lemoine, A., Hargreaves, G.M. & Bismuth, H. (2000) Transjugular intrahepatic portosystemic shunt (TIPS) for severe veno-occlusive disease of the liver following bone

marrow transplantation. *Bone Marrow Transplantation*, **25**, 987–992.

Barkholt, L., Remberger, M., Hassan, Z., Fransson, K., Omazic, B., Svahn, B.M., Karlsson, H., Brune, M., Hassan, M., Mattsson, J. & Ringdén, O. (2008) A prospective randomized study using N-acetyl-L-cysteine for early liver toxicity after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, **41**, 785–790.

Bartelink, I.H., van Kesteren, C., Boelens, J.J., Egberts, T.C., Bierings, M.B., Cuvelier, G.D., Wynn, R.F., Slatter, M.A., Chiesa, R., Danhof, M. & Knibbe, C.A. (2012) Predictive performance of a busulfan pharmacokinetic model in children and young adults. *Therapeutic Drug Monitoring*, **34**, 574–583.

Bearman, S.I. (1995) The syndrome of hepatic veno-occlusive disease after marrow transplantation. *Blood*, **85**, 3005–3020.

Bearman, S.I., Anderson, G.L., Mori, M., Hinds, M.S., Shulman, H.M. & McDonald, G.B. (1993a) Venoocclusive disease of the liver: development of a model for predicting fatal outcome after marrow transplantation. *Journal of Clinical Oncology*, **11**, 1729–1736.

Bearman, S.I., Shen, D.D., Hinds, M.S., Hill, H.A. & McDonald, G.B. (1993b) A phase I/II study of prostaglandin E1 for the prevention of hepatic venocclusive disease after bone marrow transplantation. *British Journal of Haematology*, **84**, 724–730.

Bearman, S.I., Lee, J.L., Barón, A.E. & McDonald, G.B. (1997) Treatment of hepatic venocclusive disease with recombinant human tissue plasminogen activator and heparin in 42 marrow transplant patients. *Blood*, **89**, 1501–1506.

Benya, E.C., Sivit, C.J. & Quinones, R.R. (1993) Abdominal complications after bone marrow transplantation in children: sonographic and CT findings. *American Journal of Roentgenology*, **161**, 1023–1027.

Berti, F., Rossoni, G., Biasi, G., Buschi, A., Mandelli, V. & Tondo, C. (1990) Defibrotide, by enhancing prostacyclin generation, prevents endothelin-1 induced contraction in human saphenous veins. *Prostaglandins*, **40**, 337–350.

Bordigoni, P., Witz, F., Von Bueltzingsloewen, A., Schmitt, C. & Sommelet, D. (1991) Prostaglandin E1 (PGE1) induced arthritis following bone marrow transplantation. *British Journal of Haematology*, **78**, 138–139.

van den Bosch, M.A. & van Hoe, L. (2000) MR imaging findings in two patients with hepatic veno-occlusive disease following bone marrow transplantation. *European Radiology*, **10**, 1290–1293.

Bredeson, C., Le-Rademacher, J., Zhu, X., Burkart, J., Kato, K., Armstrong, E., Sun, Y., Smith, A., Ho, T., McCarthy, P.L., Cooke, K.R., Rizzo, J.D. & Pasquini, M.C. (2013) Improved Survival with Intravenous Busulfan (IV BU) Compared to Total Body Irradiation (TBI)-Based Myeloablative Conditioning Regimens: a CIBMTR Prospective Study. *Biology of Blood and Marrow Transplantation*, **19** (suppl), S110–S111.

Brown, B.P., Abu-Yousef, M., Farner, R., LaBrecque, D. & Gingrich, R. (1990) Doppler sonography: a noninvasive method for evaluation of hepatic venocclusive disease. *American Journal of Roentgenology*, **154**, 721–724.

Bulley, S.R., Strahm, B., Doyle, J. & Dupuis, L.L. (2007) Defibrotide for the treatment of hepatic veno-occlusive disease in children. *Paediatric Blood & Cancer*, **48**, 700–704.

Cappelli, B., Chiesa, R., Evangelio, C., Biffi, A., Roccia, T., Frugnoli, I., Biral, E., Noè, A., Fossati, M., Finizio, V., Miniero, R., Napolitano, S., Ferrua, F., Soliman, C., Ciceri, F., Roncarolo, M.G. & Marktel, S. (2009) Absence of VOD in paediatric thalassaemic HSCT recipients using defibrotide prophylaxis and intravenous Busulfan. *British Journal of Haematology*, **147**, 554–560.

Carreras, E., Grañena, A., Navasa, M., Bruguera, M., Marco, V., Sierra, J., Tassies, M.D., García-Pagán, J.C., Martí, J.M., Bosch, J., Rodes, J. & Rozman, C. (1993) Transjugular liver biopsy in BMT. *Bone Marrow Transplantation*, **11**, 21–26.

Carreras, E., Bertz, H., Arcese, W., Vernant, J.P., Tomás, J.F., Hagglund, H., Bandini, G., Esperou, H., Russell, J., de la Rubia, J., Di Girolamo, G., Demuynck, H., Hartmann, O., Clausen, J., Ruutu, T., Leblond, V., Iriondo, A., Bosi, A., Ben-Bassat, I., Koza, V., Gratwohl, A. & Apperley, J.F. (1998) Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. *Blood*, **92**, 3599–3604.

Cesaro, S., Pillon, M., Talenti, E., Toffolutti, T., Calore, E., Tridello, G., Strugo, L., Destro, R., Gazzola, M.V., Varotto, S., Errigo, G., Carli, M., Zanesco, L. & Messina, C. (2005) A prospective survey on incidence, risk factors and therapy of hepatic veno-occlusive disease in children after hematopoietic stem cell transplantation. *Haematologica*, **90**, 1396–1404.

Chalandon, Y., Roosnek, E., Mermillod, B., Newton, A., Ozsahin, H., Wacker, P., Helg, C. & Chapuis, B. (2004) Prevention of veno-occlusive disease with defibrotide after allogeneic stem cell transplantation. *Biology of Blood and Marrow Transplantation*, **10**, 347–354.

Chopra, R., Eaton, J.D., Grassi, A., Potter, M., Shaw, B., Salat, C., Neumeister, P., Finazzi, G., Iacobelli, M., Bowyer, K., Prentice, H.G. & Barbui, T. (2000) Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. *British Journal of Haematology*, **111**, 1122–1129.

Clift, R.A., Bianco, J.A., Appelbaum, F.R., Buckner, C.D., Singer, J.W., Bakke, L., Bensinger, W.I., Bowden, R.A., McDonald, G.B. & Schubert, M. (1993) A randomized controlled trial of pentoxifylline for the prevention of regimen-related toxicities in patients undergoing allogeneic marrow transplantation. *Blood*, **82**, 2025–2030.

Coccheri, S., Biagi, G., Legnani, C., Bianchini, B. & Grauso, F. (1988) Acute effects of defibrotide, an experimental antithrombotic agent, on fibrinolysis and blood prostanoids in man. *European Journal of Clinical Pharmacology*, **35**, 151–156.

Coppell, J.A., Richardson, P.G., Soiffer, R., Martin, P.L., Kernan, N.A., Chen, A., Guinan, E., Vogelsang, G., Krishnan, A., Giralt, S., Revta, C., Carreau, N.A., Iacobelli, M., Carreras, E., Ruutu, T., Barbui, T., Antin, J.H. & Niederwieser, D. (2010) Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biology of Blood and Marrow Transplantation*, **16**, 157–168.

Corbacioglu, S., Greil, J., Peters, C., Wulffraat, N., Laws, H.J., Dilloo, D., Straham, B., Gross-Wieltsch, U., Sykora, K.W., Ridolfi-Lüthy, A., Basu, O., Gruhn, B., Güngör, T., Mihatsch, W. & Schulz, A.S. (2004) Defibrotide in the treatment of children with veno-occlusive disease (VOD): a retrospective multicentre study demonstrates therapeutic efficacy upon early intervention. *Bone Marrow Transplantation*, **33**, 189–195.

Corbacioglu, S., Hönig, M., Lahr, G., Stöhr, S., Berry, G., Friedrich, W. & Schulz, A.S. (2006) Stem cell transplantation in children with infantile osteopetrosis is associated with a high incidence of VOD, which could be prevented with defibrotide. *Bone Marrow Transplantation*, **38**, 547–553.

Corbacioglu, S., Cesaro, S., Faraci, M., Valteau-Couanet, D., Gruhn, B., Rovelli, A., Boelens, J.J., Hewitt, A., Schrum, J., Schulz, A.S., Müller, I., Stein, J., Wynn, R., Greil, J., Sykora, K.W., Matthes-Martin, S., Führer, M., O'Meara, A., Toporski, J., Sedlacek, P., Schlegel, P.G., Ehlert, K., Fasth, A., Winiarski, J., Arvidson, J., Mauz-Körholz, C., Ozsahin, H., Schrauder, A., Bader, P., Massaro, J., D'Agostino, R., Hoyle, M., Iacobelli, M., Debatin, K.M., Peters, C. & Dini, G. (2012) Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial. *Lancet*, **379**, 1301–1309.

DeLeve, L.D., McCuskey, R.S., Wang, X., Hu, L., McCuskey, M.K., Epstein, R.B. & Kanel, G.C. (1999) Characterization of a reproducible rat model of hepatic veno-occlusive disease. *Hepatology*, **29**, 1779–1791.

DeLeve, L.D., Shulman, H.M. & McDonald, G.B. (2002) Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Seminars in Liver Disease*, **22**, 27–42.

DeLeve, L.D., Valla, D.C. & Garcia-Tsao, G. (2009); American Association for the Study Liver Diseases. Vascular disorders of the liver. *Hepatology*, **49**, 1729–1764.

Dignan, F., Gujral, D., Ethell, M., Evans, S., Treleaven, J., Morgan, G. & Potter, M. (2007) Prophylactic defibrotide in allogeneic stem cell transplantation: minimal morbidity and zero mortality from veno-occlusive disease. *Bone Marrow Transplantation*, **40**, 79–82.

Dumont, Ch., Lambert, M. & Van Beers, B.E. (2004) MR imaging findings in a patient with

hepatic veno-occlusive disease. *Acta Gastro-enterologica Belgica*, **67**, 236–238.

Echart, C.L., Graziadio, B., Somaini, S., Ferro, L.I., Richardson, P.G., Fareed, J. & Iacobelli, M. (2009) The fibrinolytic mechanism of defibrotide: effect of defibrotide on plasmin activity. *Blood Coagulation & Fibrinolysis*, **20**, 627–634.

Erturk, S.M., Mortelé, K.J., Binkert, C.A., Glickman, J.N., Oliva, M.R., Ros, P.R. & Silverman, S.G. (2006) CT features of hepatic venoocclusive disease and hepatic graft-versus-host disease in patients after ematopoietic stem cell transplantation. *American Journal of Roentgenology*, **186**, 1497–1501.

Essell, J.H., Schroeder, M.T., Harman, G.S., Halvorson, R., Lew, V., Callander, N., Snyder, M., Lewis, S.K., Allerton, J.P. & Thompson, J.M. (1998) Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine*, **128**, 975–981.

Falanga, A., Vignoli, A., Marchetti, M. & Barbui, T. (2003) Defibrotide reduces procoagulant activity and increases fibrinolytic properties of endothelial cells. *Leukemia*, **17**, 1636–1642.

Ferrà, C., de Sanjosé, S., Lastra, C.F., Martí, F., Mariño, E.L., Sureda, A., Brunet, S., Gallardo, D., Berlanga, J.J., García, J. & Grañena, A. (1997) Pentoxifylline, ciprofloxacin and prednisone failed to prevent transplant-related toxicities in bone marrow transplant recipients and were associated with an increased incidence of infectious complications. *Bone Marrow Transplantation*, **20**, 1075–1080.

Forrest, D.L., Thompson, K., Dorcas, V.G., Couban, S.H. & Pierce, R. (2003) Low molecular weight heparin for the prevention of hepatic veno-occlusive disease (VOD) after hematopoietic stem cell transplantation: a prospective phase II study. *Bone Marrow Transplantation*, **31**, 1143–1149.

Gluckman, E., Jolivet, I., Scrobohaci, M.L., Devergie, A., Traineau, R., Bourdeau-Esperou, H., Lehn, P., Faure, P. & Drouet, L. (1990) Use of prostaglandin E1 for prevention of liver veno-occlusive disease in leukaemic patients treated by allogeneic bone marrow transplantation. *British Journal of Haematology*, **74**, 277–281.

Goldberg, S.L., Shubert, J., Rao, A.K., Redei, I., Klumpp, T.R. & Mangan, K.F. (1996) Treatment of hepatic veno-occlusive disease with low-dose tissue plasminogen activator: impact on coagulation profile. *Bone Marrow Transplantation*, **18**, 633–636.

Hágglund, H., Ringdén, O., Ericzon, B.G., Duraj, F., Ljungman, P., Lönnqvist, B., Winiarski, J. & Tydén, G. (1996) Treatment of hepatic venoocclusive disease with recombinant human tissue plasminogen activator or orthotopic liver transplantation after allogeneic bone marrow transplantation. *Transplantation*, **62**, 1076–1080.

Hägglund, H., Remberger, M., Klaesson, S., Lönnqvist, B., Ljungman, P. & Ringdén, O. (1998) Norethisterone treatment, a major risk-factor for veno-occlusive disease in the liver after allogeneic bone marrow transplantation. *Blood*, **92**, 4568–4572.

Hashiguchi, M., Okamura, T., Yoshimoto, K., Ono, N., Imamura, R., Yakushiji, K., Ogata, H., Seki, R., Otsubo, K., Oku, E., Kuroiwa, M., Higuchi, M., Kato, K., Taniguchi, S., Gondo, H., Shibuya, T., Nagafuji, K., Harada, M. & Sata, M. (2005) Demonstration of reversed flow in segmental branches of the portal vein with hand-held color Doppler ultrasonography after hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, **36**, 1071–1075.

Haussmann, U., Fischer, J., Eber, S., Scherer, F., Seger, R. & Gungor, T. (2006) Hepatic veno-occlusive disease in pediatric stem cell transplantation: impact of pre-emptive antithrombin III replacement and combined antithrombin III/defibrotide therapy. *Haematologica*, **91**, 795–800.

Herbetko, J., Grigg, A.P., Buckley, A.R. & Phillips, G.L. (1992) Venoocclusive liver disease after bone marrow transplantation: findings at duplex sonography. *American Journal of Roentgenology*, **158**, 1001–1005.

Hogan, W.J., Maris, M., Storer, B., Sandmaier, B.M., Maloney, D.G., Schoch, H.G., Woolfrey, A.E., Shulman, H.M., Storb, R. & McDonald, G.B. (2004) Hepatic injury after nonmyeloablative conditioning followed by allogeneic hematopoietic cell transplantation: a study of 193 patients. *Blood*, **103**, 78–84.

Hommeyer, S.C., Teefey, S.A., Jacobson, A.F., Higano, C.S., Bianco, J.A., Colacurcio, C.J. & McDonald, G.B. (1992) Venocclusive disease of the liver: prospective study of US evaluation. *Radiology*, **184**, 683–686.

Imran, H., Tleyjeh, I.M., Zirakzadeh, A., Rodriguez, V. & Khan, S.P. (2006) Use of prophylactic anticoagulation and the risk of hepatic veno-occlusive disease in patients undergoing hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Bone Marrow Transplantation*, **37**, 677–686.

Jones, R.J., Lee, K.S., Beschorner, W.E., Vogel, V.G., Grochow, L.B., Braine, H.G., Vogelsang, G.B., Sensenbrenner, L.L., Santos, G.W. & Saral, R. (1987) Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation*, **44**, 778–783.

Kaleelrahman, M., Eaton, J.D., Leeming, D., Bowyer, K., Taberner, D., Chang, J., Scarffe, J.H. & Chopra, R. (2003) Role of plasminogen activator inhibitor-1 (PAI-1) levels in the diagnosis of BMT-associated hepatic veno-occlusive disease and monitoring of subsequent therapy with defibrotide (DF). *Hematology*, **8**, 91–95.

Lassau, N., Leclère, J., Auperin, A., Bourhis, J.H., Hartmann, O., Valteau-Couanet, D., Benhamou, E., Bosq, J., Ibrahim, A., Girinski, T., Pico, J.L. & Roche, A. (1997) Hepatic veno-occlusive disease after myeloablative treatment and bone marrow transplantation: value of gray-scale and Doppler US in 100 patients. *Radiology*, **204**, 545–552.

Lee, J.L., Gooley, T., Bensinger, W., Schiffman, K. & McDonald, G.B. (1999) Veno-occlusive disease of the liver after busulfan, melphalan, and thiotepa conditioning therapy: incidence, risk factors, and outcome. *Biology of Blood and Marrow Transplantation*, **5**, 306–315.

Lee, J.H., Lee, K.H., Lee, J.H., Kim, S., Seol, M., Park, C.J., Chi, H.S., Kang, W., Kim, S.T., Kim, W.K. & Lee, J.S. (2002) Plasminogen activator inhibitor-1 is an independent diagnostic marker as well as severity predictor of hepatic veno-occlusive disease after allogeneic bone marrow transplantation in adults conditioned with busulfan and cyclophosphamide. *British Journal of Haematology*, **118**, 1087–1094.

Mahgerefteh, S.Y., Sosna, J., Bogot, N., Shapira, M.Y., Pappo, O. & Bloom, A.I. (2011) Radiologic imaging and intervention for gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *Radiology*, **258**, 660–671.

Marsa-Vila, L., Gorin, N.C., Laporte, J.P., Labopin, M., Dupuy-Montbrun, M.C., Fouillard, L., Isnard, F. & Najman, A. (1991) Prophylactic heparin does not prevent liver veno-occlusive disease following autologous bone marrow transplantation. *European Journal of Haematology*, **47**, 346–354.

McCarville, M.B., Hoffer, F.A., Howard, S.C., Goloubeva, O. & Kauffman, W.M. (2001) Hepatic veno-occlusive disease in children undergoing bone-marrow transplantation: usefulness of sonographic findings. *Paediatric Radiology*, **31**, 102–105.

McDonald, G.B., Sharma, P., Matthews, D.E., Shulman, H.M. & Thomas, E.D. (1984) Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology*, **4**, 116–122.

McDonald, G.B., Hinds, M.S., Fisher, L.D., Schoch, H.G., Wolford, J.L., Banaji, M., Hardin, B.J., Shulman, H.M. & Clift, R.A. (1993) Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Annals of Internal Medicine*, **118**, 255–267.

Mertens, R., Brost, H., Granzen, B. & Nowak-Göttl, U. (1999) Antithrombin treatment of severe hepatic veno-occlusive disease in children with cancer. *European Journal of Pediatrics*, **158** Suppl 3:S154–S158

Morris, J.D., Harris, R.E., Hashmi, R., Sambrano, J.E., Gruppo, R.A., Becker, A.T. & Morris, C.L. (1997) Antithrombin-III for the treatment of chemotherapy-induced organ dysfunction following bone marrow transplantation. *Bone Marrow Transplantation*, **20**, 871–878.

Mortelé, K.J., Van Vlierberghe, H., Wiesner, W. & Ros, P.R. (2002) Hepatic veno-occlusive disease: MRI findings. *Abdominal Imaging*, **27**, 523–526.

Myers, K.C., Lawrence, J., Marsh, R.A., Davies, S.M. & Jodele, S. (2013) High-dose methylprednisolone for veno-occlusive disease of the liver in pediatric hematopoietic stem cell transplant recipients. *Biology of Blood and Marrow Transplantation*, **19**, 500–503.

Ohashi, K., Tanabe, J., Watanabe, R., Tanaka, T., Sakamaki, H., Maruta, A., Okamoto, S., Aotsuka, N., Saito, K., Nishimura, M., Oh, H., Matsuzaki, M., Takahashi, S. & Yonekura, S. (2000) The Japanese multicenter open randomized trial of ursodeoxycholic acid prophylaxis for hepatic veno-occlusive disease after stem cell transplantation. *American Journal of Hematology*, **64**, 32–38.

Or, R., Nagler, A., Shpilberg, O., Elad, S., Naparstek, E., Kapelushnik, J., Cass, Y., Gillis, S., Chetrit, A., Slavin, S. & Eldor, A. (1996) Low molecular weight heparin for the prevention of veno-occlusive disease of the liver in bone marrow transplantation patients. *Transplantation*, **61**, 1067–1071.

Ouachée-Chardin, M., Elie, C., de Saint Basile, G., Le Deist, F., Mahlaoui, N., Picard, C., Neven, B., Casanova, J.L., Tardieu, M., Cavazzana-Calvo, M., Blanche, S. & Fischer, A. (2006) Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. *Pediatrics*, **117**, e743–e750.

Park, S.H., Lee, M.H., Lee, H., Kim, H.S., Kim, K., Kim, W.S., Jung, C.W., Im, Y.H., Yoon, S.S., Kang, W.K., Park, K., Park, C.H. & Kim, S.W. (2002) A randomized trial of heparin plus ursodiol vs. heparin alone to prevent hepatic veno-occlusive disease after hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, **29**, 137–143.

Peres, E., Kintzel, P., Dansey, R., Baynes, R., Abidi, M., Klein, J., Ibrahim, R.B. & Abella, E. (2008) Early intervention with antithrombin III therapy to prevent progression of hepatic venoocclusive disease. *Blood Coagulation & Fibrinolysis*, **19**, 203–207.

Pihusch, M., Wegner, H., Goehring, P., Salat, C., Pihusch, V., Hiller, E., Andreesen, R., Kolb, H.J., Holler, E. & Pihusch, R. (2005) Diagnosis of hepatic veno-occlusive disease by plasminogen activator inhibitor-1 plasma antigen levels: a prospective analysis in 350 allogeneic hematopoietic stem cell recipients. *Transplantation*, **80**, 1376–1382.

Reiss, U., Cowan, M., McMillan, A. & Horn, B. (2002) Hepatic venoocclusive disease in blood and bone marrow transplantation in children and young adults: incidence, risk factors, and outcome in a cohort of 241 patients. *Journal of Pediatric Hematology Oncology*, **24**, 746–750.

Richardson, P.G., Elias, A.D., Krishnan, A., Wheeler, C., Nath, R., Hoppensteadt, D., Kinchla, N.M., Neuberg, D., Waller, E.K., Antin, J.H., Soiffer, R., Vredenburgh, J., Lill, M., Woolfrey, A.E., Bearman, S.I., Iacobelli, M., Fareed, J. & Guinan, E.C. (1998) Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. *Blood*, **92**, 737–744.

Richardson, P.G., Murakami, C., Jin, Z., Warren, D., Momtaz, P., Hoppensteadt, D., Elias, A.D., Antin, J.H., Soiffer, R., Spitzer, T., Avigan, D., Bearman, S.I., Martin, P.L., Kurtzberg, J., Vredenburgh, J., Chen, A.R., Arai, S., Vogelsang, G., McDonald, G.B. & Guinan, E.C. (2002) Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. *Blood*, **100**, 4337–4343.

Richardson, P., Tomblyn, M., Kernan, N., Brochstein, J., Mineishi, S., Termuhlen, A., Arai, S., Grupp, S., Guinan, E., Martin, P.L., Corbacioglu, S., Holler, E., D'Agostino, R., Massaro, J., Hannah, A., Iacobelli, M. & Soiffer, R.J. (2009) Defibrotide (DF) in the Treatment of Severe Hepatic Veno-Occlusive Disease (VOD) with Multi-Organ Failure (MOF) Following Stem Cell Transplantation (SCT): Results of a Phase 3 Study Utilizing a Historical Control. *Blood (ASH Annual Meeting Abstracts)*, **114**, 654.

Richardson, P.G., Soiffer, R.J., Antin, J.H., Uno, H., Jin, Z., Kurtzberg, J., Martin, P.L., Steinbach, G., Murray, K.F., Vogelsang, G.B., Chen, A.R., Krishnan, A., Kernan, N.A., Avigan, D.E., Spitzer, T.R., Shulman, H.M., Di Salvo, D.N., Revta, C., Warren, D., Momtaz, P., Bradwin, G., Wei, L.J., Iacobelli, M., McDonald, G.B. & Guinan, E.C. (2010) Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biology of Blood and Marrow Transplantation*, **16**, 1005–1017.

Richardson, P.G., Smith, A.R., Grupp, S.A. & Kernan, N.A., Arai, S., Haut, P.R., Triplett, B.M., Gillio, III, A.P. & Symons, H.J., Adams, R.H., Horn, B.N., Lucas, K. & Martin, P.L., Mineishi, S., Ball, E.D., Boyer, M., Fort, J. & Kirov, I.I., Lehmann, L.E., Madigan, C., Maglio, M.E., Massaro, J., D'Agostino, R.B., Hannah, A.L. & Tudone, E., Hume, R., Iacobelli, M. & Soiffer, R.J. and Defibrotide Study Group (2011) Defibrotide (DF) in the treatment of hepatic Veno-Occlusive Disease (VOD) in Stem Cell Transplant (SCT) and Non-SCT Patients (Pts): early intervention improves outcome - updated results of a treatment IND expanded access protocol. *Blood (ASH Annual Meeting Abstracts)*, **118**, 487.

Richardson, P.G., Smith, A.R., Kernan, N.A., Grupp, S.A., Arai, S., Triplett, B.M., Haut, P.R., Chan, K., Symons, H.J., Horn, B.N., Gillio, A.P., Boyer, M., Krishnan, A., Lehmann, L.E., Martin, P.L., Mineishi, S., Shore, T.B., Simms-Waldrip, T., Antin, J.H., Hannah, A.L., Hume, R., Tudone, E., Heringa, C. & Soiffer, R.J. and Defibrotide Study Group (2012) Results of a large prospective study on the use of Defibrotide (DF) in the treatment of hepatic Veno-Occlusive Disease (VOD) in Hematopoietic Stem Cell Transplant (HSCT). Early intervention improves outcome – updated results of a treatment IND (T-IND) expanded access protocol. *Blood (ASH Annual Meeting Abstracts)*, **120**, 738.

Ringdén, O., Remberger, M., Lehmann, S., Hentschke, P., Mattsson, J., Klaesson, S. & Aschan, J. (2000) N-acetylcysteine for hepatic veno-occlusive disease after allogeneic stem cell transplantation. *Bone Marrow Transplantation*, **25**, 993–996.

Rosenthal, J., Sender, L., Secola, R., Killen, R., Millerick, M., Murphy, L. & Cairo, M.S. (1996) Phase II trial of heparin prophylaxis for veno-occlusive disease of the liver in children undergoing bone marrow transplantation. *Bone Marrow Transplantation*, **18**, 185–191.

Ruutu, T., Eriksson, B., Remes, K., Juvonen, E., Volin, L., Remberger, M., Parkkali, T., Häggglund, H. & Ringdén, O. (2002); Nordic Bone Marrow Transplantation Group. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. *Blood*, **100**, 1977–1983.

Salat, C., Holler, E., Kolb, H.J., Reinhardt, B., Pihusch, R., Wilmanns, W. & Hiller, E. (1997) Plasminogen activator inhibitor-1 confirms the diagnosis of hepatic veno-occlusive disease in patients with hyperbilirubinemia after bone marrow transplantation. *Blood*, **89**, 2184–2188.

Sartori, M.T., Cesaro, S., Peruzzo, M., Messina, C., Saggiorato, G., Calore, E., Pillon, M., Varotto, S., Spiezia, L. & Cella, G. (2012) Contribution of fibrinolytic tests to the differential diagnosis of veno-occlusive disease complicating pediatric hematopoietic stem cell transplantation. *Pediatric Blood Cancer*, **58**, 791–797.

Schlitt, H.J., Tischler, H.J., Ringe, B., Raddatz, G., Maschek, H., Dietrich, H., Kuse, E., Pichlmayr, R. & Link, H. (1995) Allogeneic liver transplantation for hepatic veno-occlusive disease after bone marrow transplantation–clinical and immunological considerations. *Bone Marrow Transplantation*, **16**, 473–478.

Shin, N.Y., Kim, M.J., Lim, J.S., Park, M.S., Chung, Y.E., Choi, J.Y., Kim, K.W. & Park, Y.N. (2012) Accuracy of gadoxetic acid-enhanced magnetic resonance imaging for the diagnosis of sinusoidal obstruction syndrome in patients with chemotherapy-treated colorectal liver metastases. *European Radiology*, **22**, 864–871.

Shulman, H.M. & Hinterberger, W. (1992) Hepatic veno-occlusive disease–liver toxicity syndrome after bone marrow transplantation. *Bone Marrow Transplantation*, **10**, 197–214.

Shulman, H.M., Gown, A.M. & Nugent, D.J. (1987) Hepatic veno-occlusive disease after bone marrow transplantation. Immunohistochemical identification of the material within occluded central venules. *The American Journal of Pathology*, **127**, 549–558.

Shulman, H.M., Fisher, L.B., Schoch, H.G., Henne, K.W. & McDonald, G.B. (1994) Veno-occlusive disease of the liver after marrow transplantation: histological correlates of clinical signs and symptoms. *Hepatology*, **19**, 1171–1181.

Shulman, H.M., Gooley, T., Dudley, M.D., Kofler, T., Feldman, R., Dwyer, D. & McDonald, G.B. (1995) Utility of transvenous liver biopsies and wedged hepatic venous pressure measurements in sixty marrow transplant recipients. *Transplantation*, **59**, 1015–1022.

Simon, M., Hahn, T., Ford, L.A., Anderson, B., Swinnich, D., Baer, M.R., Bambach, B., Bernstein, S.H., Bernstein, Z.P., Czuczman, M.S., Slack, J.L., Wetzler, M., Herzig, G., Schriber, J. & McCarthy, P.L. Jr (2001) Retrospective multivariate analysis of hepatic veno-occlusive disease after blood or marrow transplantation: possible beneficial use of low molecular weight heparin. *Bone Marrow Transplantation*, **27**, 627–633.

Slatter, M.A., Rao, K., Amrolia, P., Flood, T., Abinun, M., Hambleton, S., Nademi, Z., Goulden, N., Davies, G., Qasim, W., Gaspar, H.B., Cant, A., Gennery, A.R. & Veys, P. (2011) Treosulfan-based conditioning regimens for hematopoietic stem cell transplantation in children with primary immunodeficiency: United Kingdom experience. *Blood*, **117**, 4367–4375.

Song, J.S., Seo, J.J., Moon, H.N., Ghim, T. & Im, H.J. (2006) Prophylactic low-dose heparin or prostaglandin E1 may prevent severe veno-occlusive disease of the liver after allogeneic hematopoietic stem cell transplantation in Korean children. *Journal of Korean Medical Science*, **21**, 897–903.

Tay, J., Tinmouth, A., Fergusson, D., Huebsch, L. & Allan, D.S. (2007) Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation. *Biology of Blood and Marrow Transplantation*, **13**, 206–217.

Teefey, S.A., Brink, J.A., Borson, R.A. & Middleton, W.D. (1995) Diagnosis of venoocclusive disease of the liver after bone marrow transplantation: value of duplex sonography. *American Journal of Roentgenology*, **164**, 1397–1401.

Ulutin, O.N. (1993) Antithrombotic effect and clinical potential of defibrotide. *Seminars in Thrombosis and Hemostasis*, **19**, Suppl 1:186–191.

Versluys, B., Bhattacharaya, R., Steward, C., Cornish, J., Oakhill, A. & Goulden, N. (2004) Prophylaxis with defibrotide prevents veno-occlusive disease in stem cell transplantation after gemtuzumab ozogamicin exposure. *Blood*, **103**, 1968.

Wadleigh, M., Richardson, P.G., Zahrieh, D., Lee, S.J., Cutler, C., Ho, V., Alyea, E.P., Antin, J.H., Stone, R.M., Soiffer, R.J. & DeAngelo, D.J. (2003) Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. *Blood*, **102**, 1578–1582.

Willmot, F.C. & Robertson, G.W. (1920) Senecio disease, or cirrhosis of the liver due to Senecio poisoning. *Lancet*, **2**, 848–849.

Zenz, T., Rössle, M., Bertz, H., Siegerstetter, V., Ochs, A. & Finke, J. (2001) Severe veno-occlusive disease after allogeneic bone marrow or peripheral stem cell transplantation–role of transjugular intrahepatic portosystemic shunt (TIPS). *Liver*, **21**, 31–36.

Appendix 1

GRADE nomenclature for assessing levels of evidence and providing recommendations in guidelines.

Strength of recommendations. Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of evidence. The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High. Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate. Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low. Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.