Review

A Symptom-Based Approach to Early Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Reshma Ramlal *

Posted Date: 29 May 2025

doi: 10.20944/preprints202505.2343.v1

Keywords: allogeneic hematopoietic stem cell transplantation; early complications; neutropenic fever; graft versus host disease; posterior reversible encephalopathy syndrome; transplant associated- thrombotic microangiopathy; sinusoidal obstructive syndrome

 doi:10.20944/preprints202505.2343.v1

Review

A Symptom-Based Approach to Early Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Reshma Ramlal

Department of Bone Marrow Transplantation and Cellular Immunotherapy,
H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; reshma.ramlal@moffitt.org;
Tel.: 813-745-5094

Abstract: Allogeneic hematopoietic stem cell transplantation (HSCT) offers curative potential for various hematologic malignant and non-malignant disorders. Improvements in supportive care, conditioning regimens and graft versus host disease (GVHD) prophylaxis has resulted in a reduction in non-relapse mortality and improved overall survival (OS). Despite this the early-post transplant period is fraught with complications that can significantly impact morbidity and mortality. This review adopts a symptom-based approach using clinical vignettes to highlight five critical early complications of allogeneic HSCT: neutropenic fever, GvHD, posterior reversible encephalopathy syndrome (PRES), transplant associated thrombotic microangiopathy (TA-TMA) and sinusoidal obstructive syndrome (SOS). Each of these conditions presents with non-specific symptoms – such as fever, hypertension, mental status changes or jaundice- requiring high clinical suspicion and timely intervention. Using clinical vignettes, we explore the pathophysiology, clinical presentation, diagnostic challenges and evidence-based management strategies for these complications. The goal is to equip clinicians with a practical framework for recognizing and managing these high-risk syndromes occurring in the early post-transplantation period.

Keywords: allogeneic hematopoietic stem cell transplantation; early complications; neutropenic fever; graft versus host disease; posterior reversible encephalopathy syndrome; transplant associated- thrombotic microangiopathy; sinusoidal obstructive syndrome

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative option for several malignant and non-malignant conditions. Improvements in supportive care, conditioning regimens, human leukocyte antigen (HLA) typing and graft versus host disease (GvHD) prophylaxis has resulted in a reduction in non-relapse mortality (NRM) and improved overall survival (OS). Despite this, HSCT remains associated with potentially- life threatening complications. Currently, transplant related mortality (TRM) is reportedly between 6- 14% at 100 days [1–3] with 60-80% of TRM occurs in the first 100 days[3]. The leading causes for the early TRM (i.e within 100 days) are infection, organ toxicity and acute graft versus host disease (aGVHD) [1,3]. These complications result from immunodeficiency, the direct toxic effects of chemotherapy or immune dysregulation. The ability to recognize and manage these complications early can be potentially lifesaving.

In this review we employ a symptoms-based approach using clinical vignettes to discuss key early HSCT complications. To complement this approach, we present a comprehensive symptom-oriented table summarizing the major early complications of allogeneic HSCT (Table 1).

 doi:10.20944/preprints202505.2343.v1

Table 1. Symptom-Based Guide to Early Post Transplant Complications [4,12–19]. Evaluation of a patient at the onset of neutropenic fever should begin with an assessment for hemodynamic instability, followed by a thorough history and physical examination must include careful inspection of the central venous catheter insertion site, skin, oral mucosa for signs of mucositis, and the perianal region for evidence of abscesses [6].

Symptom	Differential Diagnosis	Pathophysiology	Diagnostic Clues
Fever	Neutropenic bacteremia, Fungal infection	Neutropenia + mucosal disruption → ↑risk of bacteremia	Fever with neutropenia; positive blood cultures
	Engraftment Syndrome	Release of pro-inflammatory cytokines, capillary leak	Fever around time of neutrophil engraftment with weight gain, rash, pulmonary edema, negative blood cultures
Oral Mucositis	Chemotherapy/radiation toxicity	Direct endothelial injury from conditioning regimen	Painful oral ulcers; dysphagia; drooling
	Viral stomatitis	Viral reactivation (HSV)	HSV: grouped vesicles, ulcerations on lips/tongue, positive PCR or culture
Diarrhea	Conditioning chemotherapy-induced mucositis	Direct chemotoxic effect on GI epithelium	Concurrent oral mucositis. Typically occurring around D+0-21
	Infectious – Clostridium difficile colitis, CMV colitis	C. difficile toxin leads to epithelial injury and inflammation	Recent antibiotics, positive C. diff toxin
		CMV colitis – direct viral cytopathic effect	CMV viremia, biopsy with inclusion bodies
	Acute GVHD	T-cell-activation → cytokine- mediated inflammatory response → apoptosis	Profuse secretory diarrhea, occurs post engraftment (2-4 weeks post-HSCT) may be associated with skin rash, hepatic involvement – jaundice
	Medication induced (MMF, antibiotics, magnesium)	Direct epithelial injury (MMF), alteration of intestinal microbiome, osmotic effect (magnesium salts)	Symptom resolution after holding suspected medication
Altered Mental Status	PRES	CNI-induced endothelial dysfunction → vasogenic edema in posterior brain	Seizures, headaches, visual changes. MRI – posterior white matter edema
	Infectious meninoencephalitis - HSV/HHV6	Reactivation or new infection	Focal neurologic deficits, fever, Lumbar puncture: CSF pleocytosis, CSF PCR + viral pathogen, MRI – HHV6 – bilateral T2 hyperintensity in temporal lobes, hippocampus and amygdala. HSV – unilateral T2 hyperintensities in temporal lobe, orbitofrontal cortex. May have evidence of hemorrhage.
	Metabolic encephalopathy (e.g.,		

 doi:10.20944/preprints202505.2343.v1

	hepatic encephalopathy, uremic encephalopathy) Sepsis-associated encephalopathy	Ammonia/toxin accumulation	Asterixis, hyperammonemia, liver dysfunction, renal dysfunction
	Medication-induced - Opioids	Cytokine-medicated brain dysfunction	Occurring in the context of sepsis, normal brain imaging
	- Benzodiazepines	CNS depression, especially with renal/hepatic dysfunction	Sedation, confusion Hypoactive
	- Anticholinergics (diphenhydramine, promethazine) - Antifungal (e.g., voriconazole)	Enhancement of GABAergic inhibition in the CNS	Hallucinations, dry mouth
		Central muscarinic blockade	Visual disturbances, hallucinations,
		CNS penetration	
Liver Dysfunction (Jaundice)	SOS	Endothelial injury in hepatic sinusoids → venule occlusion	Weight gain, painful hepatomegaly, elevated bilirubin, ascites. Doppler US : reversed hepatic venous flow (late finding)
	Drug Induced liver injury (DILI)	Direct hepatotoxicity, idiosyncratic reaction, mitochondrial injury, impaired canalicular transport	
	Acute GVHD	Activated T cells infiltrate liver and intrahepatic bile duct → cholestatic liver injury, bile duct epithelial apoptosis	aGVHD with isolated liver involvement is rare. Typically associated with skin and gut involvement – concurrent rash and diarrhea
	Cholestasis of sepsis (cholangitis lenta)	Mediated by endotoxin, IL6, TNFα -→ hepatocyte retention of conjugated bilirubin	+ blood cultures, fever, hypotension
Hematuria	Chemotherapy induced hemorrhagic cystitis (cyclophosphamide)	Acrolein (metabolite) accumulated in bladder → urothelial cell damage	Typically 3-10 days post cyclophosphamide. UA – negative for WBC, leukocyte esterase, nitrites
	Infectious • Bacterial UTI • BK cystitis • Adenovirus cystitis	Viral cytopathic effect	UA - +nitrites, leukocyte esterase + PCR for BK, decoy cells on cytology

 doi:10.20944/preprints202505.2343.v1

Shortness of breath, cough, hemoptysis	Infectious • bacterial pneumonia, • fungal PNA • viral (CMV, RSV)	Bacterial invasion post-barrier injury Angioinvasion (fungi) Viral cytolysis	Lobar consolidation Halo sign on CT, + galactomannan (GM), + β-D-Glucan serologies CMV PCR+
	Diffuse alveolar hemorrhage (DAH)	Alveolar-capillary injury	New diffuse pulmonary infiltrates. Bloody BAL
	Idiopathic pneumonia syndrome (IPS)	Cytokine-induced pneumonitis	Sterile BAL
Delay engraftment (persistent cytopenias)	Graft Failure – Primary	Immune mediated rejection, low stem cell dose, hematopoietic microenvironment damage	Hypocellular marrow, absence of donor chimerism
	Viral (parvo B19, CMV, HHV6)	Viral marrow suppression	+ viral PCRs
	Relapse		
	Drugs (TMP-SMX, antivirals) TA-TMA	Endothelial damage + complement activation → microangiopathic hemolysis, thrombocytopenia, anemia	Coombs-negative hemolytic anemia, normal ADAMTS13 activity, elevated creatinine

HSV – Herpes Simplex Virus, PCR – Polymerase Chain Reaction, CMV -Cytomegalovirus, GVHD – graft versus host disease, PRES – posterior reversible encephalopathy syndrome, HHV6 – human herpes virus 6, CNI – calcinurin inhibitors, CSF – cerebrospinal fluid, SOS - sinusoidal obstructive syndrome, TNF-α – tumor necrosis factor – α, UTI – urinary tract infection, UA – urinalysis, PNA – pneumonia, RSV – respiratory syncytial virus, BAL – bronchoalveolar lavage, TMP-SMX – trimethoprim-sulfamethoxazole, TA-TMA – transplant associated-thrombotic microangiopathy

CASE 1

A 48-year-old man with a history of adverse risk acute myeloid leukemia (AML) in complete remission 1 (CR1) underwent a matched unrelated donor HSCT conditioned with myeloablative busulfan and fludarabine. His post-transplant prophylaxis consisted of post-transplant cyclophosphamide (PTCy), tacrolimus and mycophenolate mofetil. Seven days post-transplant he developed a fever (maximum temperature Tmax = 39.1 ^{o}C) with chills and malaise.

Vital signs: Heart Rate (HR) 110 beats per minute (BPM), blood pressure (BP) 95/60 mmHg, respiratory rate (RR) 22/minutes, oxygen saturation (SpO2) 97% on room air.

Complete blood count (CBC): White blood cell count (WBC): 0.2 x10^9/L (absolute neutrophil count (ANC) < 100/µL. Comprehensive metabolic panel (CMP) and lactic acid are within normal limits. Blood cultures, urinalysis and chest X-ray are obtained.

He is started on bolus of normal saline and Cefepime 2g intravenously is given.

48 hour later – Blood cultures return – gram negative rods – sensitivity pending.

Neutropenic Fever

 doi:10.20944/preprints202505.2343.v1

Neutropenic fever (NF) is a common and potentially life-threatening complication following HSCT. Approximately 80% of allogeneic transplant recipients will develop febrile neutropenia [4]. The vast majority of cases are of infectious etiology [5]. However, a specific causative agent is only identified in 20-25% of febrile neutropenic episodes [6,7]. In the majority of cases (40-50%) no infectious etiology is identified, and 20-30% have a clinically documented infection without an isolated pathogen.

Blood stream infections (BSI) is the most common infectious complication following HSCT. Approximately 60% of cases occur in the pre-engraftment period [8,9]. The majority of microbiologically documented infections arise from the patient's endogenous microflora. Gram positive bacteria were previously more commonly isolated in BSI in neutropenic fever than gram negative organisms. This was attributed to the widespread use of gram-negative antimicrobial prophylaxis and central venous catheters. Currently, there has been a resurgence of gram-negative bacteremia due increasing prevalence of multidrug resistant gram-negative organisms [8,10,11]. Coagulase negative staphylococcus(CoNS), viridians group streptococci and staphylococcus aureus are the most common gram-positive organisms. These organisms are of low virulence and rarely cause life-threatening infections [4]. Among the gram-negative organisms Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa are the most common [6]. These organisms have a high virulence and can rapidly progress to septic shock and death if not treated early [4]. Invasive fungal infections account for about 5-10% of BSI in the pre-engraftment phase.

Initial laboratory workup should include a complete blood count (CBC), comprehensive metabolic panel (CMP), lactate level, prothrombin time (PT), and partial thromboplastin time (PTT). Blood cultures should be obtained both peripherally and from the central line. Urinalysis and urine culture are also essential components of the initial workup. Additional diagnostic tests and imaging should be guided by the patient's symptoms. For patients presenting with respiratory symptoms, a chest CT scan is the preferred imaging modality due to its superior sensitivity compared to plain radiography [6].

Empiric antibiotic therapy with an anti-pseudomonal beta-lactam—such as cefepime, piperacillin-tazobactam, or meropenem—must be initiated promptly to reduce the risk of rapid clinical deterioration [4]. In the setting of hemodynamic instability or septic shock monotherapy is not sufficient and addition of aminoglycoside for dual gram-negative coverage or escalation of gram-negative coverage to carbapenems may be warranted. Addition of vancomycin can be considered if there is methicillin resistant staphylococcus aureus (MRSA) colonization and in cases of suspected line infection [4,7].

Case 2

A 56-year-old woman with high-risk myelodysplastic syndrome (MDS) underwent a 7/8 mismatched unrelated donor allogeneic HSCT following myeloablative conditioning with fludarabine and busulfan. GVHD prophylaxis consisted of post-transplant cyclophosphamide, tacrolimus and mycophenolate mofetil (MMF). She had neutrophil engraftment at post-transplant day 16 and was discharged from hospital on day 18. She presents on day +35 post-transplant with profuse watery diarrhea (~ 1.8 L/day), decreased appetite, abdominal pains, nausea and occasional hematochezia. 3 days prior to the onset of diarrhea she developed a generalized pruritic maculopapular rash involving < 50% of the body surface area.

Diarrhea

Diarrhea is the most common gastrointestinal complication of allogeneic transplantation [16,17]. In the pre-engraftment period diarrhea is mainly due to chemotherapy induced mucositis [16]. Infectious causes due to *Clostridioides difficile* infection (CDI) and neutropenic enterocolitis are important causes of diarrhea in this phase [20]. Post engraftment (period following neutrophil recovery), aGVHD is the leading cause of diarrhea [16,21]. Viral agents such as cytomegalovirus

 doi:10.20944/preprints202505.2343.v1

(CMV), norovirus and adenovirus are the leading infectious etiology of diarrhea in this time frame [20]. Medications such as MMF frequently used as part of GvHD prophylaxis is also an important differential diagnosis for diarrhea in the HSCT patient (see Table 1).

The patient is case 2 has an acute onset of watery diarrhea associated with rash occurring post-engraftment. The most likely diagnosis is aGVHD.

Acute GVHD

aGVHD remains a leading cause of morbidity and mortality post-HSCT. It accounts for the 2nd leading cause of death post-transplant. [22,23]. It is estimated that 30-50% of patients undergoing HSCT will develop aGVHD with 14% developing severe aGVHD [22,24]. The most common sites of involvement of aGVHD are the skin (seen in 70% of aGVHD cases), gastrointestinal track (74%) and liver (44%) [25]. In approximately 25% of aGVHD cases there is concomitant involvement of the skin, GI tract and liver.

The pathophysiology of aGVHD is thought to occur in three phases. In the first phase, tissue damage arising from the conditioning regimen results in release of pro-inflammatory cytokines such as tissue necrosis factor -alpha (TNF-α), interleukin IL-6 and IL-1. This results in activation of the host antigen presenting cells (APC) and upregulation of MHC class II expression on APCs which improves antigen presentation. In the second phase, donor CD4+ and CD8+ T cells recognize the host alloantigens. This together with the IL12 secreted by APCs, leads to donor naïve T cells polarization into T helper 1 (Th1) cells. These release proinflammatory cytokines: TNF – α, IL-2 and INF-γ. In the third phase these pro-inflammatory cytokines recruit CD8+ T cells, macrophages and NK cells into the target tissues. These produce a direct cytotoxic effect resulting in tissue damage [23,24].

Risk factors associated with an increased risk of aGVHD are HLA disparity, increased donor and recipient age, female donor to male recipient, multiparous female donors and intensity of conditioning [23,26,27]. Patient receiving peripheral blood stem cells as their graft source do not have a higher risk of aGVHD compared to those receiving bone marrow graft. This contrasts with chronic GVHD (cGVHD) where peripheral blood graft source was associated with a higher rate of cGVHD [28]. In the era of PTCy based GVHD prophylaxis it is unclear whether these factors remain a risk factor for increased rates of aGVHD.

Clinical features of aGVHD are as described in the Case 2 above. Additionally, patients may present with nausea, vomiting, decreased appetite and weight lost when there is upper GI involvement and painless jaundice with hepatic involvement [18].

aGVHD is largely a clinical diagnosis supported by histopathologic confirmation and the exclusion of other causes. Initial evaluation of the patient presenting in case 2 would include: comprehensive metabolic panel to assess bilirubin and transaminase level for concomitant liver GVHD. Stool should be tested for CDI and a wide range of gastrointestinal pathogens with the gastrointestinal multiplex pathogen panel. Additional testing for infectious etiology includes blood viral PCR for CMV and adenovirus. In patients with abdominal pain a computed tomography (CT) scan of the abdomen and pelvis should be done to evaluate for complications such as abdominal perforation, toxic megacolon, ileus and pneumatosis intestinalism [16,18].

Where there is skin involvement, a skin biopsy can be performed which may show interface dermatitis with apoptotic keratinocytes. This can also be seen in drug induced skin rashes, autoimmune skin conditions and viral exanthems.

Endoscopic evaluation with biopsy while not necessary in patients with a high pre-test probability of aGVHD as in our case, can exclude viral infections etiologies such as CMV or adenoviral colitis which is common in this patient population [16,21,23,24]. Typically, a flexible sigmoidoscopy is undertaken with upper endoscopy in patients with upper GI symptoms. Endoscopic findings include erythema or edema of the mucosa with friability and erosions seen in more severe cases [18]. Histological features suggestive of aGVHD include apoptotic epithelial cells,

 doi:10.20944/preprints202505.2343.v1

crypt dropout and karyorrhexic debris. These findings are non-specific for aGVHD and can be seen in MMF colitis, infectious etiologies and residual conditioning therapy toxicity [18,24].

aGVHD is staged by the extent of involvement of the skin, GI tract and liver. Several staging systems exist, with the Glucksberg criteria being the most used. Severity is graded form I-IV based on the organ stage scores (1-4 per organ) (see Table 2 below).

Table 2. Acute GvHD: Glucksberg Grading and Corresponding Treatment Strategies.

GvHD Grade	Skin Involvement	Liver (Bilirubin mg/d)	GI Symptoms (stool volume mL/day) [bowel movement/day]	Treatment
Grade I	Stage 1 (rash < 25% BSA) Stage 2 (rash 25-50% BSA)	None	None or (< 500) [< 3]	Observation or topical steroids
Grade II	Stage 3 (rash > 50% BSA)	Stage 1 (2-3)	Stage 1 (500-1000) [3,4]	Systemic corticosteroids
Grade III	With or without skin involvement	Stage 2 (3.1-6) Stage 3 (6-15)	Stage 2-3 (1000-1500) [5–7], cramping, nausea	Systemic corticosteroids (2mg/kg)
Grade IV	Stage 4 – bullae, exfoliation	Stage 4 (>15)	Stage 4 (>1500) [>7], severe pain, ileus	Systemic corticosteroids

The patient in Case 2 has grade IV aGVHD [abdominal pain, stool volume 1.8 liters]. This is associated with a high non-relapse mortality at 6 months of greater than 50% [29]. First line treatment is methylprednisolone 2 mg/kg in 2 divided doses [18,23]. The response rate to corticosteroids in patients with grade III-IV acute GvHD is about 30-40% at 28 days with over 60% having steroid refractory aGVHD (SR-aGVHD) [29]. Ruxolitinib is currently the only Food and Drug Administration (FDA) approved agent in the setting of SR-aGVHD. This was based on the results of the REACH2 trial which compared ruxolitinib to best available therapy (BAT) in patients with SR-aGVHD. The overall response rate at 28 days was 62% for ruxolitinib versus 39%for BAT [30]. There is no FDA approved 3rd line treatment of SR-aGVHD. Treatment options include extracorporeal photopheresis (ECP), entanercept, mesenchymal stromal cells and alpha-1-antitrypsin.

Important supportive measures in these patients include attention to fluid and electrolyte balance and parenteral nutrition. Mold active antifungal agents and anti-viral prophylaxis should be started, and surveillance viral studies should be performed since these patients are heavily immunosuppressed. Anti-diarrheal agents should be avoided in aGVHD since it reduces gut motility and can result in an ileus or toxic megacolon [18].

Case 3

A 29-year-old woman with history of adverse risk acute myeloid leukemia (AML) undergoes a matched sibling donor allogeneic transplantation in CR1. She is conditioned with myeloablative busulfan and fludarabine with post-transplant cyclophosphamide, tacrolimus and mycophenolate mofetil for graft versus host disease (GvHD) prophylaxis. Around 15 days post -transplant patient complained of persistent headaches. Non-contrasted CT scan of the head was unremarkable. She became progressively more confused and on day 18 post-transplant and was noted to have a tonic-

 doi:10.20944/preprints202505.2343.v1

clonic seizure. Brain MRI revealed multifocal areas of signal hyperintensity in the occipital lobes and cerebellum on T2 weighted sequences.

Altered Mental Status

The incidence of neurologic complications following allogeneic transplant varies between 3-44% [31]. This can be due to neurotoxic drugs, infectious organisms, metabolic encephalopathy, cerebrovascular disease and immune-related disease [15]. It may also be a systemic manifestation of other transplant complications such as sepsis, transplant associated thrombotic microangiopathy (TA-TMA) and post-transplant lymphoproliferative disease (PTLD). Clinic features of neurologic complications include seizures, altered sensorium, focal neurologic deficits and peripheral neuropathies [15].

Early neurologic complications are usually due to medications used in the conditioning regimen or GVHD prophylaxis [31]. One of the most frequent causes is calcineurin induced (CNI) neurotoxicity, which can lead to posterior reversible leukoencephalopathy (PRES) as in case 3.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a clinico-radiologic syndrome characterized by headaches, seizures, altered mental status and visual impairment with white matter vasogenic edema affecting predominantly the occipital and parietal lobes of the brain [32]. It complicates between 6-9% of HSCT [14,33] where it is typically induced by CNI. CNIs are thought to result in endothelial dysfunction resulting in disruption of the blood brain barrier leading to protein and fluid transudation in the brain. Other proposed pathophysiologic mechanisms include disruption of cerebral autoregulation and induction of cerebral vasoconstriction caused by the CNIs [14,32,33]

The patient in Case 3 represents a typical presentation of PRES. The seizures are typically single and generalized and can cause transient post-ictal deficits. Other clinical features include cortical blindness, behavioral abnormalities, hallucination, ataxia, aphasia, confusion, disorientation and asterixis [33]. Uncontrolled hypertension can also be seen. The development of PRES is associated with decreased one-year survival rates and an increased rate of death from GVHD [34].

Brain magnetic resonance imaging (MRI) is the goal standard for the diagnosis of PRES. Typical findings are symmetric vasogenic edema in the parieto-occipital lobes on fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences [35,36]. Prompt recognition and management of PRES is important to ensure a favorable prognosis. Management involves blood pressure control and prompt removal of the offending agent (typically CNI). The CNIs can be replace with alternative immunosuppression such as the m-TOR inhibitor (sirolimus) or mycophenolate mofetil [37].

Case 4

A 39-year-old woman with AML in CR1 undergoes a matched unrelated donor HSCT after myeloablative conditioning with busulfan and fludarabine. GVHD prophylaxis includes PTCy, tacrolimus and MMF. She is currently day 24 post HSCT. She initially engrafts neutrophils by day +16 but requires daily platelet transfusion support. Over the next 2 weeks, she develops new-onset hypertension and rising serum creatinine from 0.7 mg/dL pre-transplant to 1.8 mg/dL by day +30. She also requires intermittent red blood cell transfusions despite adequate reticulocyte production and no evidence of bleeding. Lactate dehydrogenase (LDH) is elevated (750 U/L), haptoglobin is undetectable, and a peripheral smear reveals schistocytes. Tacrolimus levels are within therapeutic range.

Urinalysis shows proteinuria (protein:creatinine ratio 2.1 g/g), and ADAMTS13 activity is 45%, Coombs (DAT) test is negative. A complement panel shows low CH50, and soluble C5b-9 (sC5b-9) is elevated at 480 ng/mL (normal <244 ng/mL).

 doi:10.20944/preprints202505.2343.v1

Transplant Associated-Thrombotic Microangiopathy (TA-TMA)

TA-TMA is a microvascular disorder arising from endothelial dysfunction. In the post- HSCT setting endothelial dysfunction is due to conditioning chemotherapy, drugs used for GvHD prophylaxis, viral or bacterial infection and grade II-IV aGVHD. Endothelial dysfunction results in a proinflammatory and prothrombotic milieu resulting in complement activation and microvascular thrombosis leading to organ dysfunction. TA-TMA is an early complication of HSCT and is typically diagnosed at a median of 30-60 days [19,38]. It has an incidence of about 12% in the first year post-HSCT. It is a potentially life-threatening complication with mortality rates exceeding 50% at 1-year post-HSCT It is also associated with significant morbidity and healthcare utilization [38].

Clinical features of TA-TMA include new onset hypertension, altered mental status, confusion, and headaches. In about 40-60% [19] of cases there is significant renal involvement at disease onset. Laboratory abnormalities include features of hemolysis [elevated LDH, undetectable or low haptoglobin, falling hemoglobin, increased red blood cell transfusion requirement, schistocytes on peripheral blood smear], acute renal failure, proteinuria and prolonged platelet dependent thrombocytopenia or platelet refractoriness. Due to widespread complement activation, there are elevated levels of C5b-9 (marker of terminal complement activation) [38,39]. This also leads to reduction in complement levels and total hemolytic complement activation (CH50) as seen in Case 4 above.

Several diagnostic criteria exist to establish a diagnosis of TA-TMA. Consensus recommendations recommend using the modified Jodelle criteria [38]. This requires the presence of 4 or more of 7 features at 2 different time points within 14 days: anemia, thrombocytopenia, elevated LDH, schistocytes, hypertension, sC5b-9 > upper limit of normal and random urine protein to urine creatinine ratio (rUPCR) > 1 mg/mg [38]. The patient in Case 3 has all 7 criteria.

The management of TA-TMA involves removal of the inciting factor (CNI, mTOR inhibitor), supportive measures and complement inhibition. The first step is discontinuation or dose reduction of the endothelial-toxic agent. Several newer studies have brought this practice into questions by showing a lack of effectiveness of this approach due to frequent concurrent GvHD [19,40]. Supportive care measures include aggressive blood pressure control, fluid and electrolyte management, infectious disease prophylaxis particularly against encapsulated organisms and close monitoring of renal function. Eculizumab, the monoclonal antibody directed against C5 prevents activation of the terminal complement pathway inhibiting generation of the membrane attack complex, is used as empiric treatment in high risk TA-TMA. Early initiation of eculizumab is associated with hematologic recovery and stabilization or improvement in renal function. Eculizumab is associated with an overall survival of 52-70% at 6 months compared to historical controls of 25% [19,39,41]. Long-term sequela of TA-TMA include chronic kidney disease, persistent hypertension, neurocognitive dysfunction, prolonged transfusion dependence and increase susceptibility to infections [39].

Case 5

JM is a 30-year-old woman who underwent a matched unrelated (10/10) donor transplant for poor risk AML in CR1. She received myeloablative conditioning with busulfan and fludarabine. Her graft versus host disease prophylaxis consisted of post-transplantation cyclophosphamide, tacrolimus and mycophenolate mofetil. At day +15 post-transplantation she has developed right upper quadrant abdominal pains, weight gain and icterus. Physical examination is notable for significant edema, right upper quadrant pain, hepatomegaly and jaundice. Laboratory data is notable for WBC 0.0, Total bilirubin 5.2, Indirect bilirubin 0.8, Cre 2.1, AST 230 and ALT 330.

Early hepatic complications of HSCT include sinusoidal obstructive syndrome (SOS), drug induced liver injury (DILI), infections and acute graft versus host disease (aGvHD) [12].

Sinusoidal Obstructive Syndrome (SOS)

 doi:10.20944/preprints202505.2343.v1

SOS previously called veno-occlusive disease (VOD) is a rare, life-threatening complication of HSCT, high dose chemotherapy and high dose radiation. The syndrome is characterized by weight gain, tender hepatomegaly, ascites and jaundice [12,42]. In adults, the estimated incidence of SOS is 3.3-10% [43,44]. In contrast children undergoing allogenic transplantation have a significantly higher risk of SOS with an estimated incidence of 30% [45]. SOS is associated with significant mortality rate, about 80% in patients developing multiorgan failure [46].

Risk factors associated with the development of SOS include: use of myeloablative conditioning regimen (particularly those containing busulfan, cyclophosphamide), GVHD prophylaxis consisting of the combination of tacrolimus and sirolimus), history of prior liver disease, prior treatment with gemtuzumab ozogamicin or inotuzumab ozogamicin and pre-transplantation iron overload.

The pathophysiology of SOS is due to endothelial damage from conditioning chemotherapy, cytokines released from injured tissue, and microbial products migrating through damaged mucosa. The damaged endothelial cells release multiple factors which stimulate coagulation and inhibit fibrinolysis. This results in the formation of microthrombi in the hepatic sinusoids which become further obstructed due to detachment and embolization of the damaged endothelium. Increased vascular permeability occurring due the disruption of the endothelium results in increased fluid leakage into the extravascular space of Disse leading to narrowing of the sinusoids [12,42,45]. Disruption in sinusoidal flow can result in portal hypertension, decreased hepatic venous flow and progressive hepatocellular death. This can progress rapidly into hepatorenal syndrome and multi-organ failure [12].

The clinical presentation of SOS is related to portal hypertension and includes tender hepatomegaly, ascites, hyperbilirubinemia and weight gain (as in the case 5). Symptoms typical develop within 21 days of HSCT. However, up to 26-30% of case of SOS are of late onset [47,48] SOS is a clinical diagnosis with transjugular hemodynamic studies and liver biopsy serving only as complimentary testing particular in the setting of late onset SOS/VOD. There are four widely used diagnostic criteria as shown in Table 1. While the newer described EBMT and Cairo/Cooke criteria include cases of anicteric SOS (unlike the Baltimore Criteria) and late onset SOS, it must be noted that neither of these criteria have been validated in prospective clinical trials [49,50].

Table 3. Diagnostic criteria for SOS/VOD.

Baltimore Criteria [51]	**Modified Seattle Criteria [52]**	**EBMT Criteria [49]**
		Classic SOS/VOD in the first 21 days after ASCT ➢ Bilirubin ≥ 2 mg/dl and 2 of the following must be present o Painful hepatomegaly o Weigh gain > 5% OR o Ascites Late onset SOS/VOD ➢ Classical SOS/VOD occurring beyond day 21 OR ➢ Biopsy proven SOS/VOD OR ➢ Hemodynamic or U/S evidence of SOS/VOD with ≥ 1or more of the following Bilirubin ≥ 2 mg/dl Painful hepatomegaly Weight gain > 5% OR Ascites
Serum **bili > 2 mg/dl** within **21 days of HCT** plus at least **2 of the following:** ➢ Hepatomegaly ➢ Ascites ➢ Weight gain > 5% pre-transplant	Presentation by day **20 post HSCT** of a **least 2** of the following ➢ Bilirubin > 2 mg/dl ➢ Hepatomegaly or right upper quadrant pain ➢ Weigh gain > 2%	

 doi:10.20944/preprints202505.2343.v1

Cairo/Cooke revised Criteria [50]

Any 2 of the following after HSCT	Any 1 of the following after HSCT
➢ Bilirubin ≥ 2 mg/dl ➢ Unexpected weight gain ≥ 5% compared to pre-HSCT baseline ➢ Refractory thrombocytopenia ➢ Hepatomegaly ➢ Right upper quadrant pain ➢ Ascites Reversal of port venous flow	➢ Hepatic biopsy consistent with SOS/VOD ➢ Unexplained elevated portal venous wedge pressure

EBMT – European Society for Blood and Marrow Transplantation.

Severity Grading: The EBMT developed a grading system for SOS/VOD that evaluate 5 parameters: time since development of clinical symptoms, bilirubin, transaminases, percentage weight increase and renal function). These parameters discriminate SOS into 4 different severities : mild, moderate, severe, very severe (multiorgan dysfunction) [53]. The 100-day treatment relapsed mortality for the mild, moderate and severe were not different ranging from 2.7-8.3%, however in the very severe group, this was 36.7% [54].

Pharmacologic Prophylaxis: The data surrounding the use of ursodeoxycholic acid as prophylaxis against SOS in allogeneic transplantation it equivocal [55–57], however, it was found to have a demonstratable reduction in non-relapse mortality and improvement in overall survival through reduction in severe acute GvHD of the liver and intestinal GvHD [58]. Ursodiol is therefore recommended from the start on conditioning until day 90 during allogeneic transplantation.

Treatment. Supportive measures. Fluid balance should be monitored closely. Fluid intake should be restricted and diuretic therapy administered in situations of severe volume overload. Patients who are unresponsive to diuretics may require dialysis to manage volume overload. Mild to moderate SOS usually resolves with supportive care only. In cases of very severe SOS with multiorgan failure early initiation of defibrotide therapy is warranted [59,60]. Defibrotide, is an oligonucleotide derived from porcine tissue which has antithrombotic, thrombolytic, anti-ischemic and anti-inflammatory properties. It has little systemic anticoagulant activity and carries low risk of bleeding. In a Phase 3 study defibrotide, at a dose of 25 mg/kg/day in 4 divided doses, was used in the treatment of patient with established SOS/VOD with multiorgan failure was compared to 32 historical controls. Defibrotide showed improved complete remission (CR) rate of 25.5% at day +100 compared to 12.5% for controls (95.1% CI, 3.5-34.6; p=0.0160) [61] and was associated with significantly improved OS at day +100. Median time to response to defibrotide was 34.5 days with durable responses attained in the majority of patients [61]. Defibrotide is the only drug that is approved for the management of severe SOS/VOD.

Conclusion

Early post-transplant complications account for a significant proportion of TRM and often present with overlapping, non-specfic and rapidly evolving clinical features. Prompt diagnosis and management of these complications are paramout to improving HSCT outcomes. In this review, we took a novel approach of discussing these early complications from the stand point of clinical presentation to mirror real world challenges faced by transplant clinicians at the bedside. This method encourage physicians to consider a broad differential while employing a systematic approach to narrowing the possibilities and integrate clinical data to the clinical context. Focusing on clincal presentation promotes a deeper understanding of the urgency and ambiguity inherent in managing early post-transplant complications and highlight the need for timely empiric interventions.

 doi:10.20944/preprints202505.2343.v1

Looking to the future, there is a clear need to shift from reactive to proactive approaches in managing early complications. The ability to identify patients at highest risk of these complications through the development of validated refined pre-transplant risk stratification tools including biomarkers of endothelial dysfunction, inflammation and machine learning models-hold promise in identifying patients at highest risk of complications, potentially allowing for pre-emptive approaches.

Acknowledgments: the author acknowledges the use of OpenAI's ChatGPT (GPT-4, 2025) to assist in generating the symptom-based guide table, clinical vignettes included and general support with writing and editing. All content generated by the AI was thoroughly reviewed, edited, and verified by the author for clinical accuracy and alignment with current practice guidelines.

Conflicts of Interest: Reshma Ramlal MBBS, FACP – none.

Abbreviations

The following abbreviations are used in this manuscript:

ADAMTS-13	**A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif, member 13**
aGVHD	**Acute graft versus host disease**
AML	**Acute Myeloid Leukemia**
BAL	**Bronchoalveolar lavage**
BSI	**Blood stream infection**
CDI	**Clostridioides difficile infection (CDI)**
CMV	**Cytomegalovirus**
CNI	**Calcineurin inhibitors**
CoNS	**Coagulase negative staphylococcus**
CSF	**Cerebrospinal fluid**
DAH	**Diffuse alveolar hemorrhage**
DAT	**Direct antiglobulin test**
DILI	**Drug induced liver injury**
FLAIR	**Fluid-attenuated inversion recovery (in MRI)**
GVHD	**Graft versus host disease**
HHV6	**Human herpes virus 6**
HLA	**Human leukocyte antigen**
HSCT	**Hematopoietic stem cell transplantation**
HSV	**Herpes simplex virus**
IL-6	**Interleukin 6**
IPS	**Idiopathic pneumonia syndrome**
MDS	**Myelodysplastic syndrome/neoplasia**
MMF	**Mycophenolate mofetil**
mTOR	**Mammalian Targe of Rapamycin**
NF	**Neutropenic fever**
NRM	**Non-relapse mortality**
OS	**Overall survival**
PCR	**Polymerase chain reaction**
PRES	**Posterior reversible encephalopathy syndrome**
RSV	**Respiratory syncytial virus**
rUPCR	**Random urine protein to urine creatinine ratio**
SOS	**Sinusoidal obstructive syndrome**
SR-aGVHD	**Steroid Refractory acute graft versus host disease**
TA-TMA	**Transplant associated thrombotic microangiopathy**
TNF-α	**Tumor necrosis factor α**
TRM	**Transplant related mortality**

 doi:10.20944/preprints202505.2343.v1

UA	**Urinalysis**
UTI	**Urinary tract infection**
VOD	**Veno-occlusive disease**

References

1. Styczyński, J. et al. Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors. *Bone Marrow Transplant* **55**, 126–136 (2020).
2. Hahn, T. et al. Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. *Journal of Clinical Oncology* **31**, 2437–2449 (2013).
3. Kong, S. G. et al. Early transplantation-related mortality after allogeneic hematopoietic cell transplantation in patients with acute leukemia. *BMC Cancer* **21**, (2021).
4. Nesher, L. & Rolston, K. V. I. Febrile Neutropenia in Transplant Recipients. in *Principles and Practice of Transplant Infectious Diseases* 185–198 (Springer New York, 2019). doi:10.1007/978-1-4939-9034-4_9.
5. Einsele, H. et al. Infectious complications after allogeneic stem cell transplantation: Epidemiology and interventional therapy strategies - Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* **82**, (2003).
6. Stohs, E. J., Abbas, A. & Freifeld, A. Approach to febrile neutropenia in patients undergoing treatments for hematologic malignancies. *Transplant Infectious Disease* vol. 26 Preprint at https://doi.org/10.1111/tid.14236 (2024).
7. Freifeld, A. G. et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* vol. 52 Preprint at https://doi.org/10.1093/cid/cir073 (2011).
8. Mikulska, M. et al. Blood Stream Infections in Allogeneic Hematopoietic Stem Cell Transplant Recipients: Reemergence of Gram-Negative Rods and Increasing Antibiotic Resistance. *Biology of Blood and Marrow Transplantation* **15**, 47–53 (2009).
9. Sava, M. et al. Bloodstream infections in allogeneic haematopoietic cell recipients from the Swiss Transplant Cohort Study: trends of causative pathogens and resistance rates. *Bone Marrow Transplantation* vol. 58 115–118 Preprint at https://doi.org/10.1038/s41409-022-01851-y (2023).
10. Macesic, N., Morrissey, C. O., Cheng, A. C., Spencer, A. & Peleg, A. Y. Changing microbial epidemiology in hematopoietic stem cell transplant recipients: increasing resistance over a 9-year period. *Transplant Infectious Disease* **16**, 887–896 (2014).
11. Montassier, E., Batard, E., Gastinne, T., Potel, G. & Cochetière, M. F. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. *European Journal of Clinical Microbiology & Infectious Diseases* **32**, 841–850 (2013).
12. Idilman, R. & Arat, M. Hepatic complications of allogeneic hematopoietic cell transplantation. *Turkish Journal of Hematology* vol. 25 Preprint at (2008).
13. Tajiri, K. & Shimizu, Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. *World J Gastroenterol* **14**, 6774 (2008).
14. Balaguer-Rosello, A. et al. Noninfectious Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation. *Biology of Blood and Marrow Transplantation* **25**, 1818–1824 (2019).
15. Dowling, M. R. et al. Neurologic complications after allogeneic hematopoietic stem cell transplantation: Risk factors and impact. *Bone Marrow Transplant* **53**, 199–206 (2018).
16. Castillo Almeida, N. E., Cichon, C. J. & Gomez, C. A. How I approach diarrhea in hematological transplant patients: A practical tool. *Transplant Infectious Disease* **25**, (2023).
17. Robak, K., Zambonelli, J., Bilinski, J. & Basak, G. W. Diarrhea after allogeneic stem cell transplantation: beyond graft-versus-host disease. *Eur J Gastroenterol Hepatol* **29**, 495–502 (2017).
18. Mcdonald, G. B. How I Treat How I treat acute graft-versus-host disease of the gastrointestinal tract and the liver. (2016) doi:10.1182/blood-2015.

 doi:10.20944/preprints202505.2343.v1

19. Li, A. & Sartain, S. E. Transplant-associated TMA: the conundrum of diagnosis and treatment. *Hematology* **2024**, 206–213 (2024).
20. Non, L. R. & Ince, D. Infectious Gastroenteritis in Transplant Patients. *Gastroenterol Clin North Am* **50**, 415–430 (2021).
21. Cox, G. J. et al. Etiology and outcome of diarrhea after marrow transplantation: A prospective study. *Gastroenterology* **107**, 1398–1407 (1994).
22. Pasquini, M., Wang, Z., Horowitz, M. M. & Gale, R. P. 2013 report from the Center for International Blood and Marrow Transplant Research (CIBMTR): current uses and outcomes of hematopoietic cell transplants for blood and bone marrow disorders. *Clin Transpl* 187–97 (2013).
23. NASSEREDDiNE, S., RAFEI, H., ELBAHESH, E. & TABBARA, I. Acute Graft Versus Host Disease: A Comprehensive Review. *Anticancer Res* **37**, 1547–1555 (2017).
24. Zeiser, R. & Blazar, B. R. Acute Graft-versus-Host Disease — Biologic Process, Prevention, and Therapy. *New England Journal of Medicine* **377**, 2167–2179 (2017).
25. Martin, P. J. et al. *A Retrospective Analysis of Therapy for Acute Graft-Versus-Host Disease: Initial Treatment*.
26. Nash, R. A. et al. Acute graft-versus-host disease: analysis of risk factors after allogeneic marrow transplantation and prophylaxis with cyclosporine and methotrexate. *Blood* **80**, 1838–45 (1992).
27. Jagasia, M. et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood* **119**, 296–307 (2012).
28. Anasetti, C. et al. Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors. *New England Journal of Medicine* **367**, 1487–1496 (2012).
29. MacMillan, M. L. et al. A Refined Risk Score for Acute Graft-versus-Host Disease that Predicts Response to Initial Therapy, Survival, and Transplant-Related Mortality. *Biology of Blood and Marrow Transplantation* **21**, 761–767 (2015).
30. Zeiser, R. et al. Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. *New England Journal of Medicine* **382**, 1800–1810 (2020).
31. Maffini, E. et al. Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation. *Biology of Blood and Marrow Transplantation* vol. 23 388–397 Preprint at https://doi.org/10.1016/j.bbmt.2016.12.632 (2017).
32. Sudulagunta, S. R., Sodalagunta, M. B., Kumbhat, M. & Nataraju, A. S. Posterior reversible encephalopathy syndrome(PRES). *Oxf Med Case Reports* **2017**, 43–46 (2017).
33. Maffini, E. et al. Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation. *Biology of Blood and Marrow Transplantation* vol. 23 388–397 Preprint at https://doi.org/10.1016/j.bbmt.2016.12.632 (2017).
34. Siegal, D. et al. Central Nervous System Complications after Allogeneic Hematopoietic Stem Cell Transplantation: Incidence, Manifestations, and Clinical Significance. *Biology of Blood and Marrow Transplantation* **13**, 1369–1379 (2007).
35. Masetti, R. et al. PRES in Children Undergoing Hematopoietic Stem Cell or Solid Organ Transplantation. *Pediatrics* **135**, 890–901 (2015).
36. Schmidt, V. et al. Clinical Management of Posterior Reversible Encephalopathy Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation: A Case Series and Review of the Literature. *Acta Haematol* **135**, 1–10 (2016).
37. Dulery R, Schmidt-Hieber M & Sharrack B. Neurologic Complications. in *The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies [Internet]* (eds. Sureda A, Corbacioglu S, Greco R, Kroger N & Carreras E) (Springer, 2024).
38. Schoettler, M. L. et al. Harmonizing Definitions for Diagnostic Criteria and Prognostic Assessment of Transplantation-Associated Thrombotic Microangiopathy: A Report on Behalf of the European Society for Blood and Marrow Transplantation, American Society for Transplantation and Cellular Therapy, Asia-Pacific Blood and Marrow Transplantation Group, and Center for International Blood and Marrow Transplant Research. *Transplant Cell Ther* **29**, 151–163 (2023).
39. Jodele, S. et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. *Blood* **124**, 645–653 (2014).

 doi:10.20944/preprints202505.2343.v1

40. Li, A. et al. Transplant-Associated Thrombotic Microangiopathy Is a Multifactorial Disease Unresponsive to Immunosuppressant Withdrawal. *Biology of Blood and Marrow Transplantation* **25**, 570–576 (2019).
41. Dandoy, C. E. et al. A pragmatic multi-institutional approach to understanding transplant-associated thrombotic microangiopathy after stem cell transplant. *Blood Adv* **5**, 1–11 (2021).
42. Bonifazi, F. et al. Diagnosis and Treatment of VOD/SOS After Allogeneic Hematopoietic Stem Cell Transplantation. *Front Immunol* **11**, (2020).
43. Strouse, C. et al. Defibrotide for Treatment of Severe Veno-Occlusive Disease in Pediatrics and Adults: An Exploratory Analysis Using Data from the Center for International Blood and Marrow Transplant Research. *Biology of Blood and Marrow Transplantation* **22**, 1306–1312 (2016).
44. Strouse, C. et al. Risk Score for the Development of Veno-Occlusive Disease after Allogeneic Hematopoietic Cell Transplant. *Biology of Blood and Marrow Transplantation* **24**, 2072–2080 (2018).
45. Bajwa, R. P. S. et al. Consensus Report by Pediatric Acute Lung Injury and Sepsis Investigators and Pediatric Blood and Marrow Transplantation Consortium Joint Working Committees: Supportive Care Guidelines for Management of Veno-Occlusive Disease in Children and Adolescents, Part 1: Focus on Investigations, Prophylaxis, and Specific Treatment. *Biology of Blood and Marrow Transplantation* **23**, 1817–1825 (2017).
46. Coppell, J. A. et al. Hepatic Veno-Occlusive Disease following Stem Cell Transplantation: Incidence, Clinical Course, and Outcome. *Biology of Blood and Marrow Transplantation* **16**, 157–168 (2010).
47. Mehra, V. et al. Early and late-onset veno-occlusive disease/sinusoidal syndrome post allogeneic stem cell transplantation – a real-world UK experience. *American Journal of Transplantation* **21**, 864–869 (2021).
48. Kernan, N. A. et al. Final results from a defibrotide treatment- IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Br J Haematol* **181**, 816–827 (2018).
49. Özkan, H. A. & Özkan, S. G. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation in adult patients: Diagnosis, incidence, prophylaxis, and treatment. *Transfusion and Apheresis Science* **61**, 103372 (2022).
50. Cairo, M. S., Cooke, K. R., Lazarus, H. M. & Chao, N. Modified diagnostic criteria, grading classification and newly elucidated pathophysiology of hepatic SOS/VOD after haematopoietic cell transplantation. *Br J Haematol* **190**, 822–836 (2020).
51. JONES, R. J. et al. VENOOCCLUSIVE DISEASE OF THE LIVER FOLLOWING BONE MARROW TRANSPLANTATION. *Transplantation* **44**, 778–783 (1987).
52. Mcdonald, G. B., Sharma, P., Matthews, D. E., Shulman, H. M. & Thomas, E. D. Venocclusive Disease of the Liver after Bone Marrow Transplantation: Diagnosis, Incidence, and Predisposing Factors. *Hepatology* **4**, 116–122 (1984).
53. Mohty, M. et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* **50**, 781–789 (2015).
54. Yoon, J.-H. et al. Validation of treatment outcomes according to revised severity criteria from European Society for Blood and Marrow Transplantation (EBMT) for sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD). *Bone Marrow Transplant* **54**, 1361–1368 (2019).
55. Tay, J., Tinmouth, A., Fergusson, D., Huebsch, L. & Allan, D. S. 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 (2007).
56. Essell, J. H. Ursodiol Prophylaxis against Hepatic Complications of Allogeneic Bone Marrow Transplantation. *Ann Intern Med* **128**, 975 (1998).
57. Park, S. et al. A randomized trial of heparin plus ursodiol vs heparin alone to prevent hepatic veno-occlusive disease after hematopoietic stem cell transplantation. *Bone Marrow Transplant* **29**, 137–143 (2002).
58. Ruutu, T. et al. Improved Survival with Ursodeoxycholic Acid Prophylaxis in Allogeneic Stem Cell Transplantation: Long-Term Follow-Up of a Randomized Study. *Biology of Blood and Marrow Transplantation* **20**, 135–138 (2014).
59. Richardson, P. G. et al. Earlier defibrotide initiation post-diagnosis of veno-occlusive disease/sinusoidal obstruction syndrome improves Day +100 survival following haematopoietic stem cell transplantation. *Br J Haematol* **178**, 112–118 (2017).

 doi:10.20944/preprints202505.2343.v1

60. Kernan, N. A. et al. Final results from a defibrotide treatment- <scp>IND</scp> study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Br J Haematol* **181**, 816–827 (2018).
61. Richardson, P. G. et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood* **127**, 1656–1665 (2016).