Endothelial Dysfunction-Related Post-Allogeneic Stem Cell Transplantation

Subjects: Transplantation

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The endothelium is a very active organ formed by a thin layer of heterogeneous cells that delignate the barrier between the circulating blood and other tissues. Normal function of the endothelium is of paramount clinical significance, as it plays a key role in maintaining vascular homeostasis and a balanced coagulation but also in host defense, inflammation, and angiogenesis. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only therapy with a curative potential for a variety of malignant and non-malignant diseases. The major limitation of the procedure is the significant morbidity and mortality mainly associated with the development of graft versus host disease (GVHD) as well as with a series of complications related to endothelial injury, such as sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD), transplant-associated thrombotic microangiopathy (TA-TMA), etc. Endothelial cells (ECs) are key players in the maintenance of vascular homeostasis and during allo-HSCT are confronted by multiple challenges, such as the toxicity from conditioning, the administration of calcineurin inhibitors, the immunosuppression associated infections, and the donor alloreactivity against host tissues.

endothelial cell dysfunction disease

1. Transplant-Associated Thrombotic Microangiopathy (TA-TMA)

Transplant-associated thrombotic microangiopathy (TA-TMA) constitutes one of the most severe complications of allogenic hematopoietic stem cell transplantation (allo-HSCT) and is associated with significant morbidity and mortality [1][2][3]. It is a heterogenous disease, which is characterized by aberrant complement activation, endothelial dysregulation, and microvascular hemolytic anemia [4]. Recently, a three-hit theory was proposed regarding the pathophysiology of the disease [5], which refers to: (1) endothelial vulnerability to damage and complement activation (hit 1), (2) a toxic event (such as the conditioning therapy) injuring the endothelium and initiating the complement cascade (hit 2), and (3) additional insults (such as infection, graft-versus-host disease (GvHD), etc.) exacerbating the complement activation and leading to (widespread) microthrombi formation (hit 3). It may affect any organ [6][7] but primarily the kidneys (proteinuria, hypertension, renal failure) [6][8]; the central nervous system (headache, seizures, confusion, posterior reversible encephalopathy) [9][10]; the gastrointestinal tract (abdominal pain, diarrhea, bleeding) [11][12]; and the lungs (pulmonary hypertension) [13][14]. As a result, the clinical picture is quite heterogenous and of variable severity. Multi-organ disease (MOD), requiring intensive care

monitoring and treatment, belongs to the very severe end of the spectrum and is associated with very high morbidity and mortality [6]. Overall, prognosis is poor, with case fatality varying between 50–75% [3][15][16].

The precise incidence of the disease remains unknown and varies significantly (from 0.5% to 78%), which is partly due to the lack of consensus in diagnostic criteria [9]. In the last two decades, several groups such as the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) [17] and the International Working Group (IWG) [18] have attempted to define specific diagnostic criteria for TA-TMA, but they were both found to carry significant weaknesses and limitations in a subsequent validation study by Cho et al. [19]. Another study by Shayani et al. [20] divided the patients into those with “possible” and “probable” TA-TMA based on different (the “City of Hope”) criteria, whereas Postalcioglu et al. [2], concluded that clinical TA-TMA was significantly under-recognized using these criteria, translating to poor outcomes due to the lack of prompt therapeutic intervention. Finally, Jodele et al. [7] attempted to define “high-risk” disease in a prospective pediatric study and concluded that proteinuria (>30 mg/dL) and elevated serum C5b-9 (as a marker of complement activation) were able to predict poor outcomes (84% NRM at 1 year). The criteria proposed by different study groups for the diagnosis of TA-TMA are shown in **Table 1**.

Table 1. Proposed diagnostic criteria for thrombotic microangiopathy.

Criteria	BMT-CTN, 2005	IWG, 2007	Jodele, 2014
Parameter	**All Criteria Present**	**All Criteria Present**	**≥4 of 7 Criteria Present in ≥2 Occasions in 14 Days**
Anemia or increasing RBC transfusion requirements	YES	YES	YES
New-onset thrombocytopenia, >50% decrease in PLT count, increase in PLT transfusion requirements	YES	YES	YES
Presence of schistocytes	YES (≥2 per HPF)	YES (>4%)	YES
Elevated LDH	YES	YES	YES
Decreased haptoglobin	-----	YES	-----
Hypertension	-----	-----	YES
Proteinuria	-----	-----	YES
Elevated sC5b-9	-----	-----	YES
Renal dysfunction	YES	-----	-----

Given the significant morbidity and mortality associated with TA-TMA, the identification of risk factors associated with the development of the disease had been the focus of extensive investigation since the initial description of TA-TMA as a side effect of cyclosporin in 1980 [21]. These have been roughly categorized in pre- and post-transplant risk factors as follows: (i) pre-transplant risk factors: age, mismatched donor, myeloablative conditioning,

The presence of end-organ damage is a marker of severity; renal biopsy is not required for diagnosis, but if obtained, it is then sufficient for the establishment of diagnosis.

non-malignant disorders, and history of prior allo-HSCT and (ii) post-transplant risk factors: acute GvHD, (x4-fold increase), high disease risk index, high baseline LDH, elevated CNI levels, infections (CMV, invasive aspergillosis, BK viremia, bacteremia), mammalian target of rapamycin inhibitors (mTORi), and venous thromboembolic disease [6][22]. Since most of these factors cannot be modified or avoided, a number of medications has been explored in an effort to prevent the development or minimize the severity of TA-TMA. Prophylactic ursodeoxycholic acid (UDA) was found to reduce non-relapse mortality (NRM) and severe aGvHD in a prospective randomized study, whereas statin prophylaxis, with or without the concomitant use of UDA, was proven to be safe and reduce the risk of TA-TMA, improving outcomes [5][23]. This has led several transplant centers to adopt a statin-based prophylactic approach combining UDA and pravastatin [5][24].

With regards to treatment, preventative measures (such as HLA-matched transplantation, avoidance of toxic medications, use of reduced intensity conditioning, etc.) and supportive care are of paramount importance [5][25][26]. Prompt withdrawal of CNIs is also advised as primary intervention for TA-TMA management [17] although in a study by Li et al., this approach failed to improve survival [22]. This was attributed to the exacerbation of the underlying GvHD, which is also associated with increased morbidity, underlying the need for careful consideration of alternative substitution strategies upon CNI withdrawal. The value of therapeutic plasma exchange (TPE), once the gold standard, is debatable, as low success rates (~6%) have been documented by two different studies [27][28]. Defibrotide (DF) has been associated with favorable outcomes, showing promise in the treatment of TA-TMA [29][30][31]. More interestingly, Higham et al. used DF as prophylaxis, with significantly reduced incidence of TA-TMA (4%) compared to historical values (18–40%) [32]. The pivotal role of complement activation in the pathophysiology of TA-TMA has led complement inhibitors to the top of the treatment ladder. The use of Eculizumab has been associated with significantly better response rates and overall survival, constituting it a first-line agent in many institutes [33][34]. However, it is of particular importance that Eculizumab trough and CH50 levels are closely monitored, as more intensive treatment (dose and frequency) is required for successful outcomes [35][36]. Narsoplimab, a MASP-2 inhibitor, received a breakthrough designation from the FDA in 2021 for the treatment of TA-TMA in view of the significant improvements in hematologic parameters and overall survival [6].

2. Sinusoidal Obstructive Syndrome (SOS)/Veno-Occlusive Disease (VOD)

Sinusoidal obstructive syndrome (SOS), also known as veno-occlusive disease (VOD), is a life-threatening complication occurring after high-dose chemotherapy and HSCT [37][38]. It has also been described after high-dose radiotherapy, liver transplantation, and administration of toxic agents [39][40][41]. In HSCT, the conditioning regimen causes an initial toxic injury to the sinusoidal endothelium of the liver, disrupting the endothelial cohesions and creating gaps in the sinusoidal barrier. This allows red blood cells, leukocytes, and other debris to pass through and accumulate into the Disse space, leading to dissection of the endothelial lining and downstream embolization and sinusoid flow obstruction. This results in reduced hepatic outflow and post-sinusoidal hypertension with subsequent hepato-renal syndrome and MOD [42][43].

Clinically, SOS/VOD is characterized by weight gain (unresponsive to diuretics), painful hepatomegaly, ascites, and jaundice (although anicteric cases have been reported) [44]. Its severity varies from mild/self-resolving to severe (~25–30% patients), with MOD involving the kidneys (hepatorenal syndrome), the lungs (hypoxia, pleural effusion, pulmonary infiltrates), and the central nervous system (encepathopathy) [45]. MOD is associated with very high mortality rates (up to 80%), imperatively constituting the need to identify predictive factors for severe disease.

Several risk factors for SOS/VOD have been identified in recent years and are broadly divided into patient- and transplant-related as follows: (i) patient-related: older age, Karnofsky score <90%, pre-existing liver disease, impaired liver function tests (transaminases >×2 upper limit of normal (ULN) and bilirubin >×1.5 ULN, advanced disease, thalassemia, prior transplant, abdominal or hepatic radiation, metabolic syndrome, and raised ferritin and (ii) transplant-related: allogenic transplant, unrelated donor, HLA-mismatched donor, T-cell replete transplant, and myeloablative conditioning (containing either busulfan or total body irradiation) [46][47]. The use of novel immunotherapies for the treatment of acute leukemias, such as gemtuzumab ozogamicin and inotuzumab ozogamicin, have also been linked to the development of SOS/VOD, necessitating particular vigilance when using those agents pre-transplant [48][49].

The incidence of SOS/VOD after allo-HSCT varies significantly (from 5% to 67%) owing to different patient cohorts and transplant procedures and to different diagnostic criteria applied in different centers [45][50]. It usually develops within the first 21 days after allo-HSCT although in 15–20% patients, it may occur later [51]. Historically, the diagnosis of SOS/VOD was based on the appliance of either of the Baltimore or the modified Seattle criteria [52][53]. Although both require that patients must be within 3 weeks post transplant and include common manifestations of the disease, the main difference between the two is the inclusion of hyperbilirubinemia, which is included but not required in the Seattle criteria. Several studies have supported the use of modified Seattle criteria versus the Baltimore criteria in regard to SOS/VOD prediction, implying that waiting for hyperbilirubinemia to develop may allow progression to more severe disease, leading to worse outcomes [54][55]. In view of the aforementioned conflicting definitions leading to delayed diagnosis with significant impact on outcomes, along with the increased frequency of late-onset SOS/VOD due to the reduced intensity conditioning and the alternative donors used, the EBMT consortium established the updated EBMT criteria for SOS/VOD diagnosis in pediatric and adult populations [56][57]. The EBMT diagnostic criteria include an early and a late-onset SOS/VOD, with histology and imaging (ultrasound) having a key role in establishing the diagnosis itself. They also proposed criteria for severity grading (mild, moderate, severe, and very severe) once the diagnosis is made. This was validated in a subsequent study of 203 patients confirming significantly higher TRM in very severe SOS/VOD although further validation may be required [58].

With regards to the treatment of SOS/VOD, supportive care with close clinical monitoring (as rapidly developing disease) and timely initiation of defibrotide (DF) therapy are of paramount importance. Supportive care includes daily reports of weight, urinary output, abdominal circumference, etc., as well as therapeutic measures to comfort the patient (such as diuresis, paracentesis or thoracentesis, oxygen and analgesic therapy, etc.) [47]. Defibrotide, an oligonucleotide with anti-thrombotic, anti-inflammatory, and anti-ischemic activity, is the only approved drug for the treatment of SOS/VOD [59]. The dose of 25 mg/kg/day was evaluated in a multicenter phase III study, which

showed significantly higher CR rates (24% vs. 9%) and day +100 OS rates (38% vs. 25%) in the treatment group, without any differences in the side-effect profile [56]. This dose was further validated in a multicenter prospective study confirming that the use of 25 mg/kg/day, for at least 21 days and until resolution of symptoms, was associated with the best outcomes with the least toxicity [60]. With regards to timing of DF treatment, several studies have proposed that prompt initiation of DF is associated with better outcomes [61][62]. It is therefore recommended that patients with moderate SOS/VOD should be considered for DF treatment, whereas patients with mild disease should be closely monitored in case of deterioration.

In terms of prophylaxis, ursodeoxycholic acid (UDA) has been associated with a significant reduction of SOS/VOD incidence in various randomized studies [63][64][65]. The use of DF as a prophylactic agent has also been shown to reduce the incidence of VOD/SOS in high-risk patients by several studies [66], whereas a systematic review by Zhang et al. confirmed the lower relative risk of SOS/VOD with DF prophylaxis (risk ratio 0.47, 95% CI) [67]. A more recent meta-analysis by Cobacioglu et al. confirmed a low incidence of SOS/VOD following IV DF prophylaxis regardless of age group, supporting the use of DF in the prevention of SOS/VOD [66]. However, a prospective phase III study of DF prophylaxis for SOS/VOD (NCT02851407) stopped enrolment after meeting the criteria for futility although analyses are ongoing and are awaited with great interest.

3. Lung Injury Syndromes

Idiopathic pneumonia syndrome (IPS) was defined in 1993 in a workshop organized by the National Institute of Health as the result of widespread alveoli injury with multi-lobar pulmonary infiltrates and symptoms related to respiratory failure.

IPS may present with a variety of clinical symptoms depending on the site of lung injury. However, the typical presentation is that of acute interstitial pneumonitis. Other manifestations include diffuse alveolar hemorrhage (DAH) and peri-engraftment respiratory distress syndrome (PERDS) [68][69][70][71][72]. **Table 2** shows the clinical features of lung injury syndromes, while the criteria used for the differential diagnosis between these syndromes are presented in **Figure 1**.

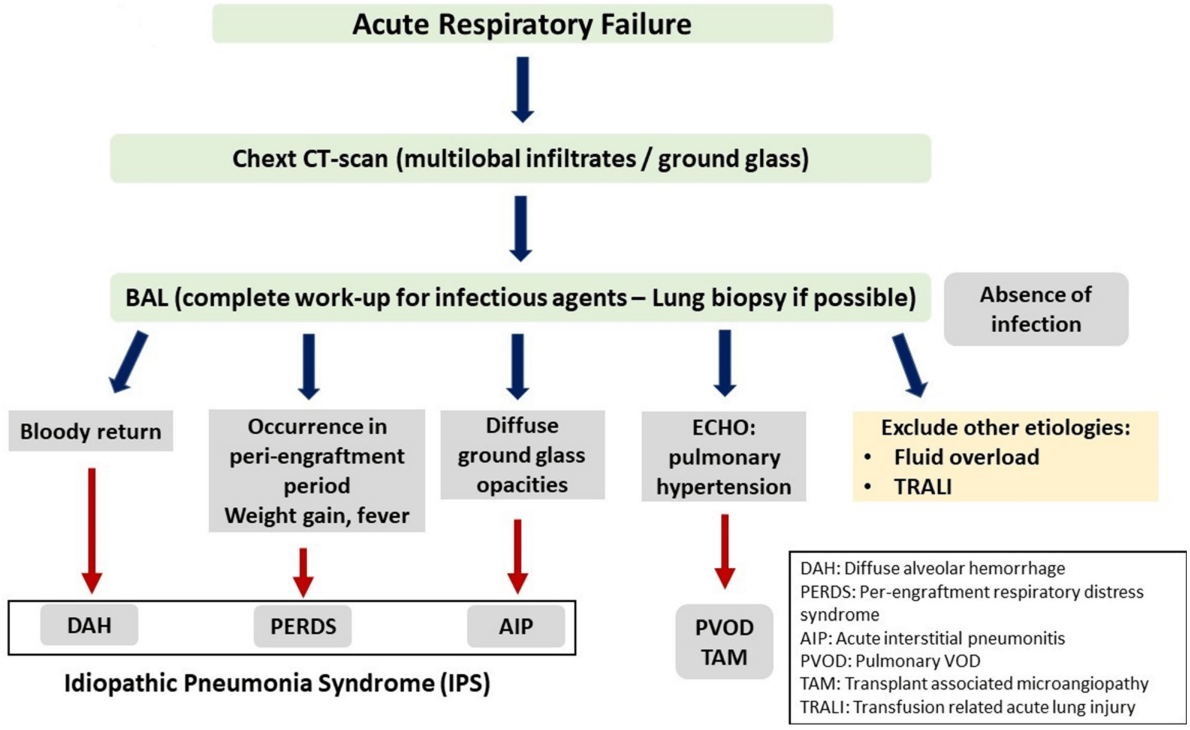

Figure 1. Idipathic Pneumonia Syndrome.

Table 2. Clinical features of acute lung injury syndromes post stem cell transplantation.

Characteristic	Idiopathic Pneumonia Syndrome	Diffuse Alveolar Hemorrhage	Peri-Engraftment Respiratory Distress Syndrome
Epidemiology	More common after allo-SCT	Equal incidence after Auto and allo-SCT	More common after auto-SCT
Median time of onset	30–40 days after allo-SCT	20–25 days after SCT	From 3 days before to 7 days after engraftment
Relation to engraftment	No relation	No relation	Occurs during the peri-engraftment phase
Clinical features	Rapid progression to respiratory failure	Progressively bloodier aliquots of bronchoalveolar lavage	Systemic manifestations such as fever, rash
Pathology	Diffuse alveolar damage	Diffuse alveolar damage	Diffuse alveolar damage
Pathogenetic drivers *	TNFα	Various cytokines	GM-CSF, G-CSF
Response to corticosteroids	Poor, some response after anti-TNF agents	Moderate response to high dose steroids	Excellent response

3.1. Idiopathic Pneumonia Syndrome

Characteristic	Idiopathic Pneumonia Syndrome	Diffuse Alveolar Hemorrhage	Peri-Engraftment Respiratory Distress Syndrome
Prognosis [73][74]	Favorable	Moderate to Poor	Very poor

* TNFα, tumor necrosis factor α; GM-CSF, granulocyte monocyte colony stimulating factor; G-CSF, granulocyte colony stimulating factor.

IPS after autologous HSCT is a different entity with probably different pathogenesis, which tends to occur later post transplant and has a favorable response to corticosteroids [78][79].

Previous studies have proposed the following risk factors to be associated with the development of IPS after allo-HSCT: (1) intensity of the conditioning, (2) total body irradiation as part of the conditioning, (3) presence of acute GVHD, (4) older age of the recipient, and (5) diagnosis of acute myeloid leukemia or myelodysplastic syndrome [80][81].

Although the pathogenesis of IPS after allo-HSCT remains elusive, it is thought to be the result of microvascular endothelial and alveolar epithelial cell injury, which is mediated by the toxicity of the conditioning regimen in combination with the immune damage induced by alloreactive donor T cells [82][83][84][85].

3.2. Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a distinct subtype of IPS characterized by progressive accumulation of red blood cells in BAL samples and/or more than 20% of hemosiderin laden alveolar macrophages in at least 30% of the alveolar spaces [86]. Clinically, DAH is characterized by rapid respiratory deterioration unless adequately treated [87]. However, the presence of alveolar hemorrhage is not synonymous to the DAH syndrome since it may be observed in the context of lung injury due to various causes, such as lung infections. It is therefore necessary to perform a complete and comprehensive work up for the presence of an occult infection prior to the establishment of diagnosis [88]. Although the median time of DAH onset is 20–30 days post graft infusion, it usually develops at a median of two weeks post engraftment, suggesting that the neutrophils are key players in the disease pathogenesis [89]. The incidence of DAH is equal between allo-SCT and auto-SCT and occurs in approximately 5–10% of patients [90]. Risk factors associated with the development of DAH after transplantation are: (1) the graft source (DAH is observed more frequently with the use of cord blood); (2) the intensity of the conditioning, with myeloablative conditioning and/or the administration of TBI being the most important high-risk factors; (3) the older age of the recipient; and (4) the occurrence of primary graft failure or the delayed engraftment of neutrophils and/or platelets [87][88][91]. Recently, a DAH case in a healthy stem cell donor possibly associated with granulocyte colony stimulating factor (G-CSF) administration was reported and raised concerns regarding the contribution of G-CSF in the pathogenetic process [92].

With regards to pathogenesis, it has been suggested that the syndrome is the result of an initial alveolar injury mediated by the toxicity of the conditioning regimen that is further aggravated during engraftment by the inflammatory potential of neutrophils and monocytes infiltrating the lung. Increased levels of various cytokines such

as IL-12, G-CSF, and TNF-α and of lipopolysaccharides in BAL samples have been associated with the development of DAH in patients after transplantation [93][94]. However, due to the absence of large studies, the exact pathogenesis of DAH in the setting of stem cell transplantation remains largely unknown.

No specific treatment is available for DAH, and its therapy is largely based on the empirical use of high-dose corticosteroids [95] owing to the suspected role of inflammation in the pathogenetic process. However, the efficacy of steroids is less than modest, and the exact dose is still a matter of debate [96]. Supportive care early in the course of the disease is of paramount importance and includes platelet transfusions and hemostatic factors such as aminocaproic acid and recombinant factor VIIa. Despite all efforts, the overall mortality rate remains high and ranges from 60% to 100% [97][98][99].

3.3. Peri-Engraftment Respiratory Distress Syndrome

Peri-engraftment respiratory distress syndrome (PERDS) is a manifestation of acute lung injury that occurs in the setting of hematopoietic stem cell transplantation [100]. It is a severe form of engraftment syndrome (ES), which is a systemic capillary leak syndrome occurring at the peri-engraftment period, defined as the period within 3 days before and 7 days after neutrophil reconstitution. PERDS is characterized by hypoxemia and bilateral pulmonary infiltrates as a result of non-cardiogenic pulmonary edema [101][102]. The incidence of PERDS varies widely from as low as 2% to as high as 20% due to differences in the diagnostic criteria but also mostly due to the various patient populations included in the existing clinical studies [101][102][103].

Risk factors associated with the development of PERDS are: (1) female sex, (2) the source of the graft (most common after PBSC than bone marrow grafts), (3) the intensity of pre-transplant chemotherapy (the less the intensity, the higher the probability of developing PERDS), and (4) the use of GM-CSF for accelerating engraftment [104][105][106]. PERDS is observed more frequently after auto-HSCT than allo-HSCT and more often after auto-HSCT for autoimmune diseases. [107].

PERDS usually presents in the context of ES and is commonly associated with systemic inflammatory clinical and laboratory signs such as fever, skin rash, weight gain, due to fluid retention, and elevated C-reactive protein. The exact pathogenetic mechanism of PERDS has not been fully elucidated. However, existing data support the role of activated myeloid cells, including neutrophils and monocytes, as the major players in the pathogenetic process. Activated myeloid cells infiltrate the lung and secrete a cocktail of proinflammatory cytokines including IL-1β, IL-2, and IL-6 that induce endothelial cell damage in the lung microvasculature. [108]. The administration of GM-CSF after graft infusion is associated with faster recovery of activated myeloid and dendritic cells that contribute to the induction of capillary leak syndrome [109].

PERDS is generally associated with a favorable prognosis. It has an excellent response to corticosteroids although many mild cases tend to resolve spontaneously. Data from previous studies showed increased incidence of acute

GVHD and increased mortality in the first year after transplant in patients with a previous diagnosis of ES/PERDS [110].

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