Acute Complications in Stem Cell Transplantation

Sumeet Mirgh and Navin Khattry

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S. Mirgh
Adult Hematolymphoid and BMT, Tata Memorial Hospital
ACTREC, Mumbai, Maharashtra, India

N. Khattry
Department of Medical Oncology and Bone Marrow Transplantation, Tata Memorial Hospital, Mumbai, Maharashtra, India

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Abstract

Hematopoietic stem cell transplantation (HSCT) remains an effective method for treating a multitude of malignant or non-malignant disorders. While in autologous HSCT, patients receive their own stem cells after myeloablation, allogeneic HSCT implies using stem cells derived from a donor. It is often a last curative option, however, associated with a considerable risk of early and long-term complications. Acute complications determine the future course of illness, have a bearing on chronic complications, and overall quality of life. Similar to acute graft-versus-host disease,
complications till day+100 posttransplant are included under acute complications. These include endothelial pathologies like engraftment syndrome (ES), transplant-associated thrombotic microangiopathy (TA-TMA), veno-occlusive disease of liver (VOD), capillary leak syndrome, and others which include non-infectious pulmonary complications, posterior reversible encephalopathy syndrome (PRES), infections (bacterial/fungal/viral), acute graft-versus-host disease (aGVHD), mucositis, and graft failure. It is important to recognize these complications at the earliest, for implementing suitable interventions, salvaging the graft and to prevent any disease relapse.

**Keywords**

Hematopoietic stem cell transplant · Engraftment syndrome · Steroids · Capillary leak · Thrombotic microangiopathy · Sinusoidal obstruction syndrome · Veno-occlusive disease · Idiopathic pulmonary syndrome · Diffuse alveolar hemorrhage · Posterior reversible encephalopathy syndrome · Mucositis · Graft failure · Chimerism · G-CSF

**Abbreviations**

ADAMTS13  | A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADCC        | Antibody-mediated cellular cytotoxicity
ADV         | Adenovirus
aGVHD       | Acute graft-versus-host disease
AML         | Acute myeloid leukemia
ARDS        | Acute respiratory distress syndrome
ASCT        | Autologous stem cell transplant
BAL         | Bronchoscopic alveolar lavage
BEAM        | BCNU (Carmustine), Etoposide, Ara-C (Cytarabine), Melphalan
BOS         | Bronchiolitis obliterans syndrome
CBT         | Cord blood transplant
CDC         | Complement-dependent cytotoxicity
CLS         | Capillary leak syndrome
CMV         | Cytomegalovirus
CNIs        | Calcineurin inhibitors
COP         | Cryptogenic organizing pneumonia
CSA         | Cyclosporine A
CY/TBI      | Cyclophosphamide/Total-body irradiation
DAH         | Diffuse alveolar hemorrhage
DFS         | Disease-free survival
DLI         | Donor lymphocyte infusion
DPTS        | Delayed pulmonary toxicity syndrome
ES          | Engraftment syndrome
FDA         | Food and Drug Administration
GCSF        | Granulocyte colony stimulating factor
HSCT        | Hematopoietic stem cell transplantation
HSV         | Herpes simplex virus
IPS         | Idiopathic pneumonia syndrome
IVIg        | Intravenous immunoglobulin
KGF         | Keratinocyte growth factor
LDH         | Lactate dehydrogenase
MAC         | Myelo-ablative conditioning
MASCC-ISOO  | Multinational association of supportive ablative conditioning
MEL         | Melphalan
MM          | Multiple myeloma
MODS/       | Multiorgan dysfunction/failure
MOF         | 
MRI         | Magnetic resonance imaging
NCI         | National Cancer Institute
CTCAEv5.0   | Common Terminology Criteria for Adverse Events
NMA         | Nonmyeloablative
NRM         | Nonrelapse mortality
OS          | Overall survival
PAI-1       | Plasminogen activator inhibitor – 1
PAP         | Pulmonary alveolar proteinosis
PCT         | Procalcitonin
PCT         | Pulmonary cytolytic thrombi
POEMS Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes
PRES Posterior reversible encephalopathy syndrome
PTLD Posttransplant lymphoproliferative disease
REG3α Regenerating islet-derived 2-alpha
RIC Reduced intensity conditioning syndrome
SOS Sinusoidal obstruction syndrome
SPI Solid-phase immunoassays
ST-2 Suppressor of tumorigenicity-2
TA-TMA Transplant-associated thrombotic microangiopathy
TBI Total body irradiation
TIPS Transjugular intrahepatic portosystemic shunt
TNF Tumor necrosis factor
TPE Therapeutic plasma exchange
TPN Total parenteral nutrition
TPO-RAs Thrombopoietin receptor agonists
TRALI Transfusion-associated acute lung injury
VOD Veno-occlusive disease of liver
vWF von-Willebrand factor
WHO World Health Organization

Acute Complications Post HSCT

For simplicity of understanding, acute complications posttransplant have been divided into endothelial, infective, acute GVHD, and others (Table 1).

Endothelial Complications

A group of complications sharing many common characteristics occur after transplant:

• Early after HSCT (between day 0 and day +100).
• Diagnosis is usually based on the presence of overlapping clinical manifestations (“ Syndromes”).
• Pathophysiologically, they begin at the capillary level in a systemic way or in one or more affected organs.
• If not properly treated, they can evolve into an irreversible multiorgan dysfunction/failure (MODS/MOF).

Table 1 Summary of acute complications post hematopoietic stem cell transplant (HSCT)

Basic pathophysiology | Complications
--- | ---
1. Endothelial | A. Systemic –
Engraftment syndrome,
Capillary leak syndrome,
TA-TMA (transplant associated
Thrombotic microangiopathy)
B. Organ-specific –
VOD (veno-occlusive disease)
Noninfectious pulmonary complications
PRES (posterior reversible
encephalopathy)
2. Infective | Refer “Cross-References” section
3. Acute GVHD | 
4. Others | Graft failure
Oral mucositis

Adapted from Carreras et al. (2019)
There is a complex interplay between the “pro-inflammatory” and “pro-thrombotic” state secondary to endothelial damage. Hence, all are clubbed together in one group. “Idiopathic pneumonia syndrome” was formerly included in this group. There is increasing evidence that GVHD is also consequent to endothelial dysfunction. Hence, GVHD might be incorporated in this group in the near future (Carreras et al. 2019). Table 1 summarizes the endothelial complications. The organ-specific complications, however, begin in a single organ, but affect systemically.

### Incidence and Risk Factors

ES is classically observed after autologous HSCT. However, it has also been described after NMA (nonmyeloablative) Allo-SCT and CBT (cord blood transplant). The incidence ranges between 5% and 50%, depending on the study population and criteria for diagnosis (Carreras et al. 2019). Risk factors for development of ES include:

- Diseases: Breast cancer, lymphomas other than Hodgkin lymphoma, POEMS, multiple sclerosis (Spitzer 2015).
- Female gender (possible) (Cornell et al. 2015; Gorak et al. 2005; Sheth et al. 2018).
- Growth factors (GM-CSF > GCSF) (possible) (Cornell et al. 2015).
- Phenotype of CD34+ donor cells (↑ expression of GATA-2, CD130, ↓ CXCR4).
- Chemotherapy (Cornell et al. 2015).
  - MM (Multiple Myeloma): Previous exposure to Bortezomib/Lenalidomide.
  - POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, skin changes): Prior cyclophosphamide exposure associated with reduced risk of ES.
  - In general, less aggressive chemotherapy associated with increased risk of ES
- Intensity of the conditioning (NMA < MEL < BEAM < CY/TBI) (Carreras et al. 2019).

Although the incidence of ES is similar irrespective of age (both children and adults), there may be considerably more NRM in children compared with adults (Spitzer 2015). ES in Allo-SCT has been variably reported between 10% and 22% in adults, and 17–48% in children. Gorak et al. reported older recipient age, female gender, and treatment with amphotericin-B, as factors associated with development of ES. In contrast to Auto-HSCT, NRM was significantly higher among Allo-SCT patients with ES (Gorak et al. 2005). As per one study in 217 adult Allo-SCT recipients, there was a strong association in the development of acute GVHD before day 28, in patients who developed ES (Omer et al. 2014). However, due to lack of standard definitions of
ES, there is no clear data to prove that ES impacts the DFS or OS (Spitzer 2015).

**Clinical Features**

The first description of ES was in 1995 by Lee et al., when they retrospectively analyzed 248 patients of Auto-SCT and observed the development of non-infectious fever and rash, at a median of 7 days post stem cell infusion (Lee et al. 1995). The clinical manifestations typically include fever, i.e., high grade, but importantly well tolerated, without any clinical/microbiological documentation or improvement with antimicrobial therapy. This fever accompanies rash (maculopapular rash mimicking GVHD) and signs of vascular leak (hypotension, Noncardiogenic pulmonary edema, pleural effusions, ascites, weight gain, edema), with/without any organ dysfunction (CNS, liver, pulmonary, renal) (Carreras et al. 2019; Cornell et al. 2015; Spitzer 2015). Hence, the diagnosis of ES relies on clinical criteria as outlined in Table 2.

A syndrome mimicking ES, termed pre-engraftment syndrome (PES), has been described after umbilical cord blood transplantation and RIC transplants. It occurs at a median of 7 days, but can precede as early as 3 days, following a transplant and 4–15 days before marrow recovery. A role for granulocytes is unclear, as it usually precedes their recovery >1 week. Similar to ES, PES is also steroid responsive, which may explain an underlying immune mechanism (Spitzer 2015). Another entity is the peri-engraftment respiratory distress syndrome (PERDS). This is defined as fever >38.3 °C + evidence of pulmonary injury in the form of hypoxia and/or pulmonary infiltrates on chest radiographs (CXRs) in the absence of clinical cardiac dysfunction that has to occur within 5 days of neutrophil engraftment (Capizzi et al. 2001).

There have been no head-to-head comparisons of both criteria. However, as per literature (including an Indian study), there is evidence that Maiolino criteria are more sensitive, than Spitzer (Sheth et al. 2018; Carreras et al. 2010). In fact, Sheth et al. proposed a modified Maiolino criteria (Maiolino criteria with time laxity) for diagnosis of all patients with possible ES (Sheth et al. 2018). Similarly, Dispenzieri et al. observed more than 50% incidence in POEMS patients undergoing Auto-SCT, and proposed maintaining the Spitzer and Maiolino criteria but uncoupling the timing between the neutrophil recovery and clinical manifestations. Although there is no significant difference in the patterns of ES among various disorders, there is an unusually high frequency of ES in POEMS patients. This might be due to

| Table 2 | Spitzer and Maiolino criteria for diagnosis of engraftment syndrome (Carreras et al. 2019; Spitzer 2015) |
|-----------------|-----------------------------------------------------------------------------------------------------|
| Around the day when engraftment starts (i.e., first day of ANC > 500/uL) | |
| **Spitzer criteria (2001)**<br>(within 96 h of engraftment) | **Maiolino criteria (2003)** |
| **Major** | Noninfectious fever + (either of these 3; since 24 h prior or any time after engraftment): Rash or Pulmonary infiltrates or Diarrhea (at least two episodes of liquid depositions per day without any microbiological evidence) |
| 1. Temperature $\geq$38.3 °C with no identifiable infectious etiology. | |
| 2. Erythodematous rash involving $\geq$25% of body surface area and not attributable to a medication. | |
| 3. Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates and hypoxia. | |
| 4. Sudden increase in CRP values $\geq$20 mg/dL (recently included criterion). | |
| **Minor** | |
| 1. Hepatic dysfunction with either bilirubin $\geq$2 mg/dL or transaminase levels $\geq$2 times normal. | |
| 2. Renal insufficiency (serum creatinine) $\geq$2 times baseline. | |
| 3. Weight gain $\geq$2.5% of baseline body weight. | |
| 4. Transient encephalopathy unexplainable by other causes. | |
| **Diagnosis** | All three major criteria or two major criteria and one or more minor criterion, within 96 h of engraftment |
| **Comments** | More complex but specific |
| | Less specific, but simple |
an aberrant cytokine milieu in them (VEGF, TNF-α), possibly exaggerated by ASCT (Dispensieri et al. 2008).

The skin rash associated with ES has been reported more frequently reported in patients with breast cancer undergoing ASCT, compared to those with lymphoma. On the other hand, ASCT use for autoimmune disorders, since corticosteroids are regularly used as a maintenance therapy in these patients, may prophylactically reduce the risk of ES (Spitzer 2015). There are other events, similar to ES, which must be differentiated from it (refer Table 3).

**Biomarkers**

Considering the inadequacy of the clinical criteria and possible progression to MODS (in absence of timely intervention), it would be ideal to identify biomarkers which would help us to take a decision preemptively. However, data regarding the same is scarce. A recent study identified PCT (procalcitonin) <2 ng/ml as an adjunctive biomarker for identification of patients suffering from non-infectious fever associated ES post-ASCT (Knoll et al. 2019). Similarly, Elafin has been identified as an IHC stain and a new biomarker for pre-engraftment syndrome (Chacon et al. 2013). However, the former is an expensive test in a resource-limited setting, while the latter is not easily available. An Indian study showed WBC/CRP ratio >0.056, as an important inexpensive bedside tool with high specificity to identify engraftment fever from an infectious etiology (Punatar et al. 2015).

**Management**

Finally, one may believe that ES may trigger a graft-versus-tumor effect in ASCT, and consequently, lead to increased survival. However, a review of nearly 600 patients failed to show any effect of ES on relapse and survival (Cornell et al. 2013). Further studies on the pathogenesis and biomarkers which will help differentiate the ever-lasting dilemma of the relation between ES and acute GVHD are required (Fig. 1).

**Capillary Leak Syndrome (CLS)**

Idiopathic systemic capillary syndrome (also known as Clarkson disease) was initially described in healthy people who manifested with episodic crisis of hypotension, hypoalbuminemia, and severe anasarca (Carreras et al. 2019). It has been defined as weight gain >3% in 24 h and positive intake balance despite furosemide administration (Nurnberger et al. 1997). Subsequently, it has been described after administration of cytokines (IL-2, IL-4, TNF, G-CSF) and post-HSCT. Pathophysiologically, the inclusion of CLS in this group points to an underlying endothelial damage as the cause. This might be secondary to high levels of VEGF and angiopoietin-2 in such patients (Carreras et al. 2019).

**Incidence and Risk Factors**

The incidence varies between 5.4% and 21% (Lucchini et al. 2016; Nurnberger et al. 1997) and it is predominantly observed in children (Carreras et al. 2019).
Risk factors include:

1. Presence of severe infection (Lucchini et al. 2016; Boisrame-Helms et al. 2013).
2. GCSF administration.
3. CSA prophylaxis (Takatsuka et al. 2002; Deeren et al. 2005).
4. Unrelated HSCTs.
5. High-intensity conditioning or increased cumulative chemotherapy prior to the conditioning (Lucchini et al. 2016).

Diagnostic Criteria

1. Early after HSCT (≈days +10–11).
2. Unexplained weight gain >3% in 24 h.
3. Positive intake balance despite furosemide administration (at least 1 mg/kg) evaluated 24 hours after its administration (Carreras et al. 2019).

Treatment

At the earliest suspicion of CLS, stop G-CSF immediately. Steroids and aggressive supportive therapy with catecholamines, colloids, and plasma are required (Carreras et al. 2019). There is no recommendation in literature for dosing of steroids. However, Methylprednisolone has been used at a dose of 1–1.5mg/kg/day (similar to acute GVHD) (de Azevodo and Tabak 2001). In a case without any response to steroids, there was a
significant and dramatic response to Bevacizumab, thereby pointing the role of an underlying pathogenesis secondary to VEGF (Yabe et al. 2010). Importantly, CLS patients have significant high risk of developing acute GVHD at day +30. The prognosis of patients with CLS remains dismal. As per Lucchini et al. two-third patients needed admission to ICU and nearly half required invasive mechanical ventilation. The TRM in patients with CLS is eightfold than those without CLS (43% versus 5%) (Lucchini et al. 2016). We need future studies that will delineate the biological relation between sepsis, GvHD, and CLS development in terms of cytokine release and endothelial damage.

**Transplant Associated Thrombotic Microangiopathy (TA-TMA)**

**Introduction**

TMAs (thrombotic microangiopathies) comprise a heterogeneous group of disorders characterized by microangiopathic hemolytic anemia and thrombocytopenia due to platelet clumping in the microcirculation leading to ischemic organ dysfunction. In order to standardize this phenomenon, a consensus has been recently proposed by an International Working Group (as below):

**TMA**

1. TTP (thrombotic thrombocytopenic purpura).
2. HUS (hemolytic uremic syndrome).
   a. Complement mediated.
   b. Infection associated
3. Others.
   (a) Pregnancy.
   (b) DIC (disseminated intravascular coagulation).
   (c) Drugs.
   (d) Malignancies.
   (e) Connective tissue disorder.
   (f) **Transplant associated TMA** (solid organ transplant or HSCT associated).

**Incidence**

The incidence is highly variable and ranges between 0.5% and 76%. This is due to the variability of manifestations and absence of a single, uniformly accepted diagnostic criteria. Moreover, the presence of other causes of anemia, thrombocytopenia, and renal dysfunction in post-HSCT setting further confounds the picture (Jodele et al. 2015; Elemary et al. 2019).

**Pathogenesis and Risk Factors**

**Diagnosis**

The gold standard for diagnosis of microangiopathy would be an organ biopsy. However, it is not always feasible in a post-transplant immunosuppressed patient with severe thrombocytopenia. Moreover, presence of clinical and lab markers which would serve as a surrogate for evidence of microangiopathy, question the necessity of an invasive procedure. The criteria used for diagnosis are summarized in Table 4. Importantly, coagulation parameters (PT, aPTT) in all these criteria are normal, and ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity is <10% (Carreras et al. 2019) (Refer Fig. 2).

The criteria above explore the clinical and lab markers for diagnosis of TA-TMA. The BMT-CTN criteria (2005) pay more attention on the pathogenesis of microangiopathy (schistocytes, elevated LDH, ruling out immune hemolysis by a negative Coombs’ test) and systemic involvement (renal/CNS) other than hematological system, whereas IWG criteria include the focus mainly on hematological parameters with inclusion of cytopenias. The overall TMA criteria (2010) were more broad as they included both cytopenias (of IWG criteria) and microangiopathy markers (both IWG and BMT-CTN), albeit, without renal/CNS involvement (Carreras et al. 2019; Jodele et al. 2015; Elemary et al. 2019). Jodele et al., as per their experience, showed three important aspects of TA-TMA. Firstly, creatinine alone is a
very poor marker for AKI in TMA. Hence, the inclusion of proteinuria and hypertension (disproportionate to that expected from use of steroids and CNIs) as early markers of kidney injury. Moreover, CNS symptoms develop much later, as a part of severe multivisceral TMA. Lastly, they pointed out that schistocytes are evident later in the course of the disease. The description of cases with histopathological evidence of TMA, without any schistocytes on smear, refutes the norm that they are sine-qua-non in TMA (Wirtschafter et al. 2018; Murphree et al. 2019). It has been hypothesized that this might be due to increased vascular permeability and extravasation of RBCs into tissues. Hence, an acute elevation of LDH, with proteinuria and severe hypertension, were preemptive of impending TA-TMA (occurring nearly 10–14 days before diagnosis of TMA). They also included markers of complement activation, thereby giving weightage on the “second-hit” component of TA-TMA. Importantly, it has been shown that patients with proteinuria (>30 mg/dL) and markers of complement activation (elevated C5b-9 levels) have a dismal prognosis, with an 84% NRM (nonrelapse mortality) at 1 year (Jodele et al. 2015). This will not only help us in prognostication but also enable us to switch gears to an aggressive management, when either of these markers is deranged.

### Treatment

1. **Supportive therapy.**
   
   Stop CNIs (cyclosporine)/sirolimus. Treat concomitant infections, GVHD (which might be further triggers for TA-TMA), and renal replacement therapy for renal dysfunction. Watch for flare of GVHD after discontinuation of CNIs. Substitute it with MMF and/or steroids.

2. **Specific therapy.**

   a. **TPE (therapeutic plasma exchange)**

   Although initial descriptions of TPE suggested a limited benefit in hardly one-third cases with 80% mortality, recent data have suggested 59–64% CR rates. TPE was more beneficial in patients who initiated it early after diagnosis (within first 2 weeks), and those with factor H autoantibodies. Importantly, TPE use in TA-TMA is for at least 2–3 weeks, after which it can be tapered off (unlike TTP/aHUS where it is tapered off after 5 days), if there is clinical improvement. This is important as premature discontinuation can result in a flare (Carreras et al. 2019; Elemary et al. 2019). Even after initial improvement, TPE has to be tapered slowly over 3–4 weeks (Khosla et al. 2018).

| Criteria | BMT-CTN (2005) | IWG-EBMT (2007) | Cho et al. (2010) | Jodele et al. (2014) |
|----------|----------------|----------------|------------------|---------------------|
| Schistocytes | ≥2/hpf | >4% | ≥2hpf | + |
| Elevated LDH | + | + | + | + |
| Anemia/ RBC transfusion | + | + | + | + |
| Thrombocytopeniaa | + | + | + | + |
| DCT negative | + | + | + | + |
| Low haptoglobin | + | + | + | + |
| Renal/CNS dysfunctionb | + | + | + | + |
| Proteinuriac* | + | + | + | + |
| Hypertensiond | + | + | + | + |
| Increased serum C5b-9 levels* | + | + | + | + |

a = de novo/prolonged/progressive thrombocytopenia; platelet<50,000 or 50% reduction from baseline; b = Renal: Doubling of serum creatinine or 50% reduction of creatinine clearance from baseline; CNS: headaches/confusion/hallucinations/seizures; c = A random urinalysis showing urine protein concentration of ≥30 mg/dL, d = Hypertension refractory to ≥2 antihypertensive drugs; * = Presence of these two features at diagnosis indicate high-risk features associated with poor outcome

Adapted from Carreras et al. (2019), Jodele et al. (2015), Elemary et al. (2019)
b. Rituximab

Rituximab is beneficial for those with factor H autoantibodies, in combination with TPE. It has been reported to benefit 80% cases. When used with TPE, Rituximab should be administered immediately after TPE (Carreras et al. 2019). When given, it is administered at usual dose of 375 mg/m² weekly for 4 doses (Elemary et al. 2019).

c. Defibrotide

Defibrotide is a polydeoxyribonucleotide salt has been used in VOD posttransplant with variable CR rates between 30% and 60%. It is an endothelial protector that blocks action of plasminogen-activator inhibitor-1 and attenuates the effects of TNF. It has anti-thrombotic, anti-inflammatory, thrombolytic, and fibrinolytic properties (Carreras et al. 2019; Khosla et al. 2018). The response rate with defibrotide has been 55%, either as monotherapy or in combination. The dosing in TA-TMA is extrapolated from that of VOD, i.e., 6.25 mg/kg every 6 h (Jodele et al. 2015). However, Defibrotide is not available in India. It has to be imported and its prohibitive cost limits its usage. Interestingly, it has been used

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**Fig. 2** Pathogenesis and risk factors for the development of TA-TMA – “double-hit” due to endothelial and complement dysfunction. (Adapted from Carreras et al. 2019; Jodele et al. 2015).
at low doses <10 mg/kg/day as monotherapy, i.e., one-third of the approved dose and still effective (Devadas et al. 2017). This efficacy at a reduced dosage with the safety and ease of administration of Defibrotide makes it a productive option for transplant physicians.

d. Eculizumab

As per the understanding of complement activation in the pathogenesis of TA-TMA, terminal complement inhibitors such as Eculizumab, a C5 inhibitor, have come up as a promising new therapy in these patients. Responses have been documented in 67–92% patients. Dosing is similar to that of PNH, i.e., 900 mg every 2 weeks, with dose modulation as per monitoring of CH50 levels. Importantly, antimeisingococcal prophylaxis should be used from the initiation of therapy until 8 weeks after completion of therapy or till CH50 becomes normal. Compared with aHUS, eculizumab for TA-TMA typically requires a longer induction time with at least 4–6 weeks of therapy. However, it can be discontinued after TA-TMA resolution without disease relapse, and lifelong treatment is not required. It is recommended to use eculizumab as monotherapy – as concurrent use of TPE would remove eculizumab from the blood as well as replenish C5 available for activation. Intriguingly, concurrent use of eculizumab and rituximab may affect rituximab activity as the latter medication depends in part on complement activity. Other newer drugs available for the same with limited literature include interleukin-2 receptor (CD25) antibodies (basiliximab, daclizumab), NO donors (eicosapentaenoic acid, statins, transdermal isosorbide tape), TNF-α inhibitors (Infliximab), prostacyclin analogs, and bosentan (Khosla et al. 2018).

Prognosis

Jodele et al. recently reported that proteinuria ≥30 mg/dL and elevated serum C5b-C9 levels (evidence of terminal complement activation) are associated with worse prognosis, with a survival rate of <20%. These patients deserve early intervention with eculizumab (Khosla et al. 2018). Some authors believe that there are two forms of TA-TMA. One, associated with CNI (calcineurin inhibitor) and the other, unrelated to it. Whereas the former has a good prognosis, the latter has a bad prognosis and needs specific treatment (Carreras et al. 2019). In their excellent review, Khosla et al. have proposed that TMA index (LDH/platelets ratio) ≥20, schistocyte count >5–10/hpf, elevated serum creatinine, adult >18 years, and unrelated/haplo donors have a bad prognosis (Khosla et al. 2018). An Indian study recently showed that 5-year OS in patients with TA-TMA was nearly half of that for patients without TA-TMA (29% vs. 51%) (Kalantri et al. 2019).

VOD (Veno-Occlusive Disease)/SOS (Sinusoidal Obstruction Syndrome)

Introduction

Sinusoidal obstruction syndrome, formerly known as veno-occlusive disease of the liver (VOD), is the term used to designate the symptoms and signs that appear early after HSCT because of conditioning regimen-related hepatic toxicity. It is characterized by jaundice, fluid retention, and tender hepatomegaly appearing in the early (first 35–40 days) after HSCT (Carreras et al. 2019). It is a multisystem disease with an overall mortality >80%. Historically, it was initially published in veterinary literature, back in the 1920s. Subsequently, in the 1950s, it was diagnosed in humans, after bush-tea ingestion (due to pyrrolizidine alkaloids) and secondary to chemotherapy. The first evidence in the field of HSCT came in 1982 from a series of 29 patients treated with high dose mitomycin-C and autologous bone marrow transplant (Cairo et al. 2020).

Risk Factors

Incidence as per two prospective studies, for autologous HSCT varies between 3% and 6%, and for allogeneic HSCT varies between 9% and 14% (Carreras et al. 2019) (Fig. 3 and Table 5).
Diagnosis

Development of diagnostic criteria is important to enable clinicians to identify this disease entity, make the correct diagnosis promptly, and intervene appropriately. Two of these criteria have been in long use since more than two decades (Table 6). However, there are major limitations of these established diagnostic criteria:

(i) Time constraint of 21 days post-HCT.
(ii) Development of anicteric SOS/VOD (addressed in part by the modified Seattle criteria).

Chemotherapy / Radiotherapy

Activation of vascular endothelial cells

Release of heparinase

Break down of extracellular matrix proteins and disruption of cytoskeletal architecture

ECs become rounded
increase vascular permeability leak into the extravascular

Sinusoidal narrowing
(INFLAMMATION)

Vasoconstriction (endothelin-1), Angiogenesis

Hepatic stellate cell activation

Release of
a. vWF platelet aggregation
b. Tissue Factor coagulation
c. PAI-1 Inhibition of fibrinolysis

EC embolisation

Prothrombotic and hypofibrinolytic state

Microvascular clot formation
(THROMBOSIS)

Fig. 3 Pathogenesis of VOD/SOS. (Adapted from Cairo et al. 2020)
Table 5  Risk factors for VOD

| Pretransplant factors | Mild–moderate risk (3–10 times) | Severe risk (>10 times) |
|-----------------------|----------------------------------|-------------------------|
| **Unmodifiable**      | Increased recipient age; infant (<1 year). | Serum bilirubin >1.5 mg/l (>26 μmol/l) before transplantation. |
|                       | Increased serum transaminases.     | Prior gemtuzumab ozogamicin. |
|                       | High ferritin (>1000 ng/ml)b       | Prior inotuzumab ozogamicin. |
|                       | Preexisting liver disease.         | Prior norethisterone.      |
|                       | Specific disordersa                |                         |
|                       | CMV seropositivity.               |                         |
|                       | Sepsisb                           |                         |
|                       | Vancomycin use during cytoreductive therapy. |                         |
|                       | Pretransplantation acyclovir.      |                         |
|                       | Interval between diagnosis of malignancy and transplant >12 monthsb |                         |
|                       | Use parenteral alimentation.       |                         |
|                       | Genetic factors.                  |                         |
|                       | (GSTM1 polymorphism, C282Y allele, MTHFR 677CC/1298CC haplotype) |                         |
|                       | Deteriorated health status within 30 days before transplantation (diarrhea, fever, parenteral nutrition before transplant)b |                         |
|                       | Prior SCT or prior abdominal radiation. |                         |
|                       | Disease in ≥CR2.                   |                         |
|                       | Acute liver/gut GVHDb.             |                         |
| **Transplant factors**| **Conditioning:**                  |                         |
|                       | a. Myeloablative regimens          |                         |
|                       | b. Busulfan containing (vs. nonbusulfan) prior to cyclophosphamide (Bu-cy > cy-Bu) |                         |
|                       | c. TBI(>12Gy) + cyclophosphamide |                         |
|                       | d. Fludarabine-containing          |                         |
| **Transplantation:**  | Allogeneic (versus autologous) transplantation. |                         |
|                       | Non T-cell depleted graftsb        |                         |
| **GVHD prophylaxis:** | Sirolimus + methotrexate + tacrolimus. |                         |
|                       | Methotrexate + cyclosporine.       |                         |
|                       | Cyclosporine-containing.           |                         |

aSpecific disorders – specific underlying disorders [hemophagocyticlymphohistiocytosis; osteopetrosis; neuroblastoma; Wilms tumor; rhabdomyosarcoma; juvenile myelomonocytic leukemia; chronic leukemia (CML); and hemoglobinopathies (sickle-cell anemia; thalassemia) |

bRisk factors for pediatric stem cell transplants
Adapted from Cairo et al. (2020), Dalle and Giralt (2016), Mohty et al. (2020)

Table 6  Conventional diagnostic criteria for VOD

| Modified Seattle criteria (1993) | Baltimore criteria (1987) |
|----------------------------------|--------------------------|
| Development of two or more of the following events within 20 days of HCT (and without an obvious, alternative medical explanation): | Serum bilirubin >2 mg/l within 21 days of HCT, Plus at least two of the following: |
| Serum total bilirubin concentration > 2 mg/l (>34.2 micromoles/l) | Hepatomegaly |
| Hepatomegaly or right upper quadrant pain | Ascites |
| Sudden weight gain due to fluid accumulation (>2% of baseline body weight) | Weight gain >5% from pre-HCT weight (without an alternative medical explanation) |
(iii) Recent clinical descriptions that are different from those described 25 years ago.

(iv) Development of newer imaging capabilities which may be more sensitive to specific indicators of SOS/VOD.

The European Society for Blood and Marrow Transplantation (EBMT) has proposed a revised differential diagnostic criteria (below) for both children and adults, which incorporates both clinical and radiological criteria for early diagnosis of this entity. However, it should be borne in mind that anicteric VOD and refractory thrombocytopenia are typical of pediatric VOD (Cairo et al. 2020).

**EBMT Revised Criteria for VOD (Both Adults and Children)**

Any two of the following criteria following HCT:

- Elevated bilirubin (≥2 mg/l) (≥34.2 μmoles/l) or greater than upper institutional limits†.
- Unexpected weight gain (≥5% compared to baseline weight pre-HCT).
- Excessive platelet transfusions consistent with refractory thrombocytopenia post-HCT.
- Hepatomegaly for age or increase size over baseline pre-HCT.
- Right upper quadrant pain.
- Ascites confirmed by physical exam and/or imaging studies.
- Reversal of portal venous flow (hepatofugal flow) by Doppler ultrasound.

**Grading of Severity**

After diagnosis of VOD, it is imperative to grade the severity in order to prognosticate the patient in terms of outcomes. The original SOS/VOD grading classification was developed by McDonald et al. in 1993 (Cairo et al. 2020).

**McDonald Grading System of SOS/VOD**

**MILD**

- No adverse effects of liver disease.
- No treatment of fluid retention.
- No analgesic treatment of enlarged liver.
- Complete reversal of signs, symptoms, and abnormal laboratory values secondary to VOD.

**MODERATE (one or more)**

- Adverse effects of liver disease secondary to VOD.
- Treatment of fluid retention (Diuretic, fluid restriction, and/or Na⁺ restriction).
- Complete resolution of signs, symptoms, and abnormal laboratory values secondary to VOD.

**SEVERE (Both)**

- Adverse effects of liver disease secondary to VOD.
- Signs, symptoms, and abnormal laboratory values secondary to VOD that did not all normalize by Day +100 posttransplant.
- Death due to VOD.

Recently, EBMT proposed a system (Table 7) for early prognostication, which included kinetics of symptom development/bilirubin, renal function, in addition to liver functions (bilirubin, transaminases), and weight gain. However, this is for VOD in adults.

The pediatric criteria utilized the same adult criteria (as above), with the addition of ascites,
Table 7  EBMT criteria for grading of severity of VOD (Carreras et al. 2019)

|                          | Mild          | Moderate      | Severe        | Very severe  |
|--------------------------|---------------|---------------|---------------|--------------|
| Time since onset of first symptoms | >7 days       | 5–7 days      | ≤4 days       | Any-time     |
| Bilirubin (mg/dl)        | ≥2 to <3      | ≥3 to <5      | ≥5 to <8      | ≥8           |
| Bilirubin kinetics       | Doubling within 48 h |
| Transaminases (× N)      | ≤2            | >2 to ≤5      | >5 to ≤8      | >8           |
| Weight gain (%)          | <5            | ≥5 to <10⁴    | ≥5 to <10     | >10          |
| Renal function (× baseline at HSCT) | <1.2         | ≥1.2 to <1.5  | ≥1.5 to <2    | ≥2 or other data Of MOF |

If patients fulfill ≥2 criteria in two different categories, they should be classified in the most severe category. In the presence of two or more risk factors for SOS, patients should be in the upper grade.

*Weight gain ≥5% and < 10% is considered as a severe SOS. However, if the patient does not fulfill other criteria for severe SOS, it is therefore considered a moderate SOS.
†Patients with an already elevated bilirubin prior to HCT conditioning, this criterion should be excluded from diagnostic criteria.

Prophylaxis and Treatment

A. Prevention/Prophylaxis

1. Avoid modifiable risk factors
   - Reduce intensity of conditioning; use CY + BU instead of BU + Cy.
   - Pharmacologic monitoring of busulfan.
   - Avoid the use of progesterone and estrogen, if possible.
   - Treat iron overload (chelation).
   - Treat viral hepatitis.
   - Delay HSCT if active hepatitis.
   - Try to avoid CNI (if not possible use TAC instead CSA) for GVHD prophylaxis.

2. Pharmacological Prophylaxis

Recommended

1. UDCA (Ursodeoxycholic acid)
   UDCA is a hydrophobic bile acid, i.e., nontoxic to hepatocytes (unlike hydrophilic bile acids). It protects the liver by modulating release of cytokines and its immunomodulatory effects. It is recommended by EBMT and BSBMT (Carreras et al. 2019; Cairo et al. 2020). Hence, it is recommended at the start of conditioning until day 90 after transplant (Mohty et al. 2020).

2. Defibrotide
   Recommended for use in high-risk pediatric transplants, at a dose of 25 mg/kg/day. In one RCT, when used at the above dose from first day of conditioning till day +30 post-HCT, the incidence of VOD was 12% versus 20% in those who did not receive defibrotide prophylaxis (Carreras et al. 2019; Cairo et al. 2020).
Other drugs like low-molecular-weight/unfractionated heparin, antithrombin III, prostaglandin-1, and pentoxifylline are debatable, and not recommended, at present (Carreras et al. 2019).

**Treatment**

**Supportive Care**

Supportive care remains an important cornerstone of therapy. The most important aspect is to minimize extracellular fluid overload without compromising intravascular volume and renal perfusion, while maintaining weight < 5% of baseline. Hence, a hawk-eye approach to fluid intake, salt load, urine output, and daily weights remains the mainstay of supportive care. Some patients develop ascites with or without pleural effusion, or pulmonary infiltrates in the absence of ascites and become hypoxemic. Patients may require serial small volume paracentesis (to maintain renal perfusion and adequate lung volumes in children) for ascites, which is associated with discomfort or pulmonary compromise. Hemodialysis or hemofiltration may be required for patients who experience renal failure or need more invasive methods to control fluid balance during the evolution of SOS/VOD (Carreras et al. 2019; Cairo et al. 2020). In order to avoid any hepatotoxic drugs, azoles should be replaced by echinocandins, if feasible (Mohty et al. 2020).

**Defibrotide**

Defibrotide is approved by the US Food and Drug Administration and European Medicines Agency for the treatment of adults and children with SOS/VOD following HCT with renal or pulmonary dysfunction and “severe” SOS/VOD. On comparison with best supportive care, Defibrotide leads to a statistically significant improvement in day+100 survival (38% vs. 25%). It is used at a dose of 6.25 mg/kg every 6 hourly, and duration as per response (Cairo et al. 2020). No dose adjustments are needed in renal failure, while corrected body weight is needed in obese patients. Duration of Defibrotide therapy is for 14–21 days, until the resolution of all clinical features of VOD. However, it can be stopped earlier if there is a complete response. Importantly, although it is approved for severe VOD, there are recommendations for an earlier preemptive use of Defibrotide in moderate SOS/VOD. The most important adverse event associated with Defibrotide is bleeding, followed by a small risk of anaphylaxis. Some experts recommend to keep a higher platelet cut-off of 30,000 for patients on Defibrotide. Similarly, if planning any intervention, it should be withheld at least 2 h before and after the procedure (Mohty et al. 2020).

**Methylprednisolone**

It is recommended by some authors. However, its role is debatable, and no there is no defined dose (Carreras et al. 2019). Considering the increased infectious risk associated with methylprednisolone, recommendations are against its primary use in SOS (Mohty et al. 2020).

**t-PA (Tissue Plasminogen Activator)**

A small retrospective study analyzed the benefit of t-PA + heparin combination, in 42 HSCT patients. Responses occurred in 29% patients, however, at the cost of bleeding in 88% patients. Hence, it is no longer recommended due to the excessive risk of bleeding (Dalle and Giralt 2016).

**Liver Transplantation and TIPS (Transjugular Intrahepatic Portosystemic Shunt)**

Lastly, orthotopic liver transplantation and transjugular, intrahepatic, portosystemic shunts have been successfully performed in small numbers of patients with SOS/VOD (Cairo et al. 2020).

**Prognosis**

Patients with mild to moderate VOD without any evidence of multiorgan dysfunction (associated renal or pulmonary dysfunction) have a favorable prognosis. However, prognosis for patients with severe disease (accompanied by multiorgan dysfunction) is guarded. Recently, the prognosis has improved due to better supportive care and new treatment options (Cairo et al. 2020). With respect
to grading, the OS and day 100 survival rate were significantly lower in patients with very severe SOS as compared to other three groups (58% vs. 89%). Similarly, day 100 TRM (transplant-related mortality) was significantly high (more than one-third) in the very severe SOS group (36.7%) versus others (2–8%) (Mohty et al. 2020).

**Novel Trends**

We live in an era of biomarkers. Recently, markers have been identified for prognostic value, both at day 0 (L-Ficolin, HA, VCAM-1) and at diagnosis of VOD (ST2, ANG2, L-Ficolin, HA, VCAM-1) (Carreras et al. 2019). Future studies will be needed to delineate the prognostic value of these markers. Similarly, novel imaging methods like Doppler ultrasound with shear wave elastography and contrast-enhanced ultrasound may serve as innovative modalities for diagnosis of VOD (Dietrich et al. 2018).

**Noninfectious Pulmonary Syndromes**

Lung injury has been observed in 25–55% of patients post-HSCT, and this contributes to the morbidity and mortality in post-HSCT period. Due to more rampant and preemptive use of antibiotics, infectious complications have decreased, and the immune complications continue to predominate. These complications can be subdivided on the basis of their localization (Carreras et al. 2019).

**Posttransplant Noninfectious Pulmonary Complications**

**Airways**
- BOS (Bronchiolitis Obliterans Syndrome)
- COP (Cryptogenic Organizing Pneumonia)

**Lung parenchyma**
- Acute interstitial pneumonitis
- Acute respiratory distress syndrome (ARDS)
- BCNU pneumonitis
- Radiation pneumonitis
- Idiopathic Pneumonia Syndrome (IPS)
- Post-HSCT lymphoproliferative disease
- Eosinophilic pneumonia

Pulmonary alveolar proteinosis
- **Lung vasculature**
- Peri-engraftment respiratory distress syndrome (PERDS)
- Capillary leak syndrome (CLS)
- Diffuse alveolar hemorrhage (DAH)
- Pulmonary VOD
- Transfusion-associated acute lung injury (TRALI)
- Pulmonary cytolytic syndrome
- Pulmonary arterial hypertension
- Pulmonary thromboembolism (Carreras et al. 2019) (Fig. 4)

**Idiopathic Pneumonia Syndrome (IPS)**

**Definition**

Evidence of widespread/diffuse alveolar injury in the absence of any active lower respiratory tract infection, and absence of any organ dysfunction which can lead to fluid overload (cardiac/renal/iatrogenic fluid overload) (Carreras et al. 2019).

**Incidence and Risk Factors**

Fortunately, due to increased use of RIC, incidence of IPS has decreased from >20% two decades back to <10% (8% after MAC, 2% after RIC) (Carreras et al. 2019). Its incidence after autologous HSCT has been reported around 5.7% (Kantrow et al. 1997).

**Risk Factors for IPS**

- Older age.
- Karnofsky index <90.
- Higher “diagnosis-HSCT” interval.
- MAC-conditioning incorporating BCNU or TBI (≥12 Gy).
- HLA disparity.
- GVHD prophylaxis with MTX.
- Acute GVHD.
- Previous viral infection.
- Other malignancies than leukemia (Carreras et al. 2019).
Clinical Presentation

The usual presentation occurs before 120 days, most commonly between day+18 and day+21. This is, in contrast, to the commonly noticed risk period of day+40 to +50, approximately two decades back (Vande Vusse and Madtes 2017). In contrast, IPS in autologous HCT usually presents around day+63 (range: 7–336 days) (Cheng and Madtes 2017).

As expected from its name, clinical features include symptoms and signs of pneumonia: fever, dry cough, breathlessness, tachypnea, crackles/rales on chest auscultation. This is accompanied by multilobar infiltrates on chest CT, increased alveolar-arterial diffusion of oxygen, and restrictive abnormality on pulmonary function tests (Carreras et al. 2019).

Prognosis

Importantly, IPS remains an entity with poor prognosis with 60–80% mortality. If mechanical ventilation is required, >90% patients succumb to the illness (Carreras et al. 2019). Hence, in the field of HSCT, IPS remains an important complication with dire need for biomarkers which can preempt early use of steroids and newer therapies.

Pathogenesis

Management

Supportive therapy (Carreras et al. 2019)

- Airway.
  - Mechanical ventilation (invasive or not [high-flow nasal O2, CPAP])
- Breathing.
  - Supplemental O2 therapy
- Circulation.
  - Strict control of fluids balance/hemofiltration
- Others.
  - Empiric broad-spectrum antimicrobials (Fig. 5).
Definitive Therapy

1. Methylprednisolone
   Consistent with the pathogenesis, due to the marked inflammatory cytokine storm in the lungs, steroids are recommended. Methylprednisolone ≤ 2 mg/kg/day, administered early in the course of illness, should be considered as early as possible (Carreras et al. 2019). Doses more than 2 mg/kg/day have been tried and not been shown to improve any response versus doses lesser than that (Fukuda et al. 2003).

2. Etanercept
   Preclinical data has shown the significance of TNFα in pathobiology of IPS. Hence, *Etanercept* 0.4 mg/kg twice weekly (maximum of eight doses) was tried in combination with systemic steroids (2 mg/kg/day). Importantly, Yanik et al. published a randomized study of combination (etanercept + steroids) versus steroids + placebo. Although it was terminated prematurely due to slow accrual, there were no significant differences in response rates at day +28 (Yanik et al. 2014). On the other hand, the same group conducted a phase II trial in pediatric patients; more than two-third achieved a CR (71%) with a 1-year survival of 63% (Yanik et al. 2015). This combination has also been shown to be effective in exceptional cases of late IPS with 42% CR rate, and a 2-year survival of 62% among the responders (Thompson et al. 2017).

Fig. 5  Algorithm for pathogenesis of IPS. (Adapted from Vande Vusse and Madtes 2017)
3. **Investigational**
   Tocilizumab (anti IL-6) and Brodalumab (anti IL-17) are experimental agents which can be tried (Carreras et al. 2019).

4. **Others** (insufficient evidence at present)
   - **Keratinocyte growth factor (KGF):** It has been shown to protect against chemoradiation-induced epithelial damage and improves tissue repair. Mouse models have shown that KGF can limit IPS and GVHD severity.
   - **Antifibrinolytics:** Reduces bleeding and blood transfusion requirement.
   - **Defibrotide:** Since it protects against one endothelial complication (sinusoidal obstruction syndrome), it might protect against IPS too. The increased risk of bleeding limits its role.
   - **Macrolides:** When used at doses higher than used for infections, it suppresses macrophage-derived cytokines. It has been shown to improve cryptogenic organizing pneumonia in small studies, however, outside transplant setting (Vande Vusse and Madtes 2017).

**Novel Trends**

Detailed immunological evaluations have shown CD4 T h17 cells playing an important role in IPS and GVHD (Mauermann et al. 2008). Novel therapies targeting them, i.e., Halofuginone may represent an important paradigm (Sundrud et al. 2009). Schlatzer et al., using proteomics, compared peptide profiles of patients who developed IPS versus those who did not. They found lipopolysaccharide-binding protein (LBP) as a candidate molecule diagnostic for IPS and confirmed that its increasing levels could preempt the development of IPS (Schlatzer et al. 2012).

**Risk Factors**

DAH is higher in patients after TBI and high-dose Cy (Carreras et al. 2019) recipients with inherited metabolic storage disease, especially mucopolysaccharidosis (Kharbanda et al. 2006). Surprisingly, the frequency of DAH is similar among both MAC and RIC conditioning regimens, and it does not appear to have any co-relation with platelet counts (Carreras et al. 2019).

**Clinical Presentation**

It usually presents within the first month after SCT (median 23 days), particularly during the *pre-engraftment phase*. However, more than one-third cases (nearly 42%) present later in the course of posttransplant period. The clinical presentation is similar to IPS, with the exception of *hemoptysis* (in DAH) (Carreras et al. 2019). On imaging, these patients present with diffuse alveolar and interstitial infiltrates, primarily in central and basilar distribution (Vande Vusse and Madtes 2017). However, in order to differentiate it from IPS, Bronchoscopy with BAL becomes the most important modality. It is defined by the presence of (any of the following):

- Minimum 20% hemosiderin laden macrophages (may take 72 h to appear).
- Minimum 30% alveoli showing blood.
- Progressive bloodier return of BAL fluid aliquots, in at least three segmental bronchi (as a surrogate for blood in alveoli).

However, it is very difficult to differentiate infectious from noninfectious DAH, in the absence of a pathogen. Hence, infectious workup as usual should be sent during a BAL (Carreras et al. 2019, Vande Vusse and Madtes 2017).
Treatment

Methylprednisolone remains the mainstay of therapy for DAH. There have been two studies at different doses, however, with contrasting results. Wanko et al. showed that high-dose steroids (>4 mg/kg/day of methylprednisolone or equivalent) decrease mortality with better efficacy, along with addition of amino-caproic acid (ACA) (Wanko et al. 2006). On the other hand, Rathi et al. demonstrated that addition of ACA did not make a difference, irrespective of dose of methylprednisolone (Rathi et al. 2015). Hence, the best treatment is to use low-dose steroids (Methylprednisolone/C20 250 mg/day) ± ACA (Carreras et al. 2019). Similarly, addition of rVIIa has not been shown to alter time to resolution of alveolar hemorrhage, duration of mechanical ventilation, duration of oxygen supplementation, or hospital mortality. Unfortunately, it led to thrombotic events in 9% patients (Elinoff et al. 2014). Along with steroids, maintaining adequate oxygenation with supplemental oxygen is necessary. Mechanical ventilation should be avoided, if possible, and noninvasive ventilation (CPAP, BiPAP) be administered (Carreras et al. 2019).

Prognosis

Unfortunately, the prognosis of DAH remains dismal. As per one study, mortality is as high as 85% by day+100. Importantly, mortality is higher in patients with multiorgan dysfunction (>60%) and in patients who develop DAH late post-allo-SCT (70%) (Carreras et al. 2019).

C. PERDS (Discussed Under Engraftment Syndrome).
D. Delayed Pulmonary Toxicity Syndrome (DPTS).

Delayed pulmonary toxicity syndrome is a specific pulmonary complication, exclusive to autologous HCT. It is characterized by the presence of interstitial pneumonitis and fibrosis, which may delay for months to years (Carreras et al. 2019). Incidence of DPTS varies between 29% and 64% in auto-SCT recipients who receive conditioning regimens containing cyclophosphamide, cisplatin, etoposide, and bischloroethylnitrosourea (BCNU). Median time to onset is 45 days (range: 21–149 days) (Wilczynski et al. 1998). Symptoms are nonspecific and include exertional dyspnea, dry cough, and fever. Pulmonary function testing reveals a restrictive pattern with a marked reduction in the diffusion capacity (Soubani and Pandya 2010). Imaging reveals bilateral interstitial infiltrates and ground-glass opacities (Wilczynski et al. 1998). This syndrome has a favorable prognosis and response to steroids (1 mg/kg) has been noted in >90% cases. In responders, steroids are tapered over a period of 2 months (Soubani and Pandya 2010).

E. Pulmonary Cytolytic Thrombi (PCT).

This is an unusual pulmonary complication, with an unknown etiology. It is usually seen in children with GVHD, at a median time of 72 days post-HCT. Intriguingly, it presents with fever and peripheral pulmonary nodules on chest CT. Surgical lung biopsy shows necrotic, basophilic thromboembolism with entrapped monocytes. Interestingly, clinical presentations improve over 2 weeks, and radiographic findings clear over weeks (CengizSeval et al. 2018). Since this is a rare and under-reported entity, there is no proven treatment. Woodard et al. showed the benefit with 1–2 mg/kg prednisolone till resolution of primary symptoms (typically 2 weeks), followed by a taper over 2–4 weeks, with a 3-year OS 71% (Woodard et al. 2000).

F. Pulmonary Alveolar Proteinosis (PAP).

PAP is characterized by the presence of PAS-positive lipoproteins in terminal bronchioles and alveoli, due to macrophage dysfunction. Similar to congenital and autoimmune PAP, with deficiency of GM-CSF either congenitally or due to antibody respectively, secondary PAP can occur post HCT, either due to macrophage depletion or anti-GM-CSF alloantibody. Diagnosis is clinched by the presence of milky/opaque BAL fluid yielding PAS-positive material and after excluding infectious pathologies. However, lung biopsy is needed for definitive diagnosis (Vande Vusse...
and Madtes 2017). PAP may be self-limited but can progress to fatal respiratory failure. Importantly, the prognosis of PAP remains poor, and value of inhaled GM-CSF in these patients is questionable (Soubani and Pandya 2010) (Tables 8 and 9).

**PRES (Posterior Reversible Encephalopathy Syndrome)**

This entity was first described in 1996, as a syndrome with typical neurological features and imaging findings, by Hinchey et al. (1996). PRES (Posterior reversible encephalopathy syndrome) is a rare but serious complication post-allogeneic SCT. Apart from allo-SCT, it has been reported in patients with severe hypertension, eclampsia, autoimmune disorders, renal failure, sepsis (Schmidt et al. 2016; Gaziev et al. 2017), chemotherapy (Methotrexate, L-asparaginase, Adriamycin, Cyclophosphamide, Cytarabine, Vincristine), and immunosuppressants (Steroids, Cyclosporine, Tacrolimus, Rituximab, Interferon, Antithymocyte globulin (ATG), Fludarabine, Sirolimus) (Kapoor et al. 2018). Pathophysiologically, it has been hypothesized to occur due to disturbance of cerebral autoregulation or secondary to cerebral vasoconstriction. In the former, sudden development of hypertension which overwhelms cerebral autoregulation results in loss of endothelial integrity and transudation of fluid, leading to vasogenic edema. On the other hand, there is cerebral vasoconstriction leading to perfusion deficit and ischemic changes in the latter (Schmidt et al. 2016; Gaziev et al. 2017).

**Table 8** Timeline of pulmonary complications post Allo-SCT (Chi et al. 2013)

| Time duration (possible other pathologies contributing to the complication) | Pre-engraftment (<day 30) | Post-engraftment (day 30–100) | Late (>day 100) |
|-------------------------------|---------------------------|--------------------------------|-----------------|
| Pre-engraftment (<day 30) (neutropenia, mucositis, acute GVHD) | CHF | DAH (diffuse alveolar hemorrhage) | Pulmonary VOD |
| PERDS (pulmonary cytolytic thrombi) | IPS (idiopathic pneumonia syndrome) | DPTS (delayed pulmonary toxicity syndrome) | BOS (bronchiolitis obliterans syndrome) |
| PCT* | | | |
| *irrespective of timing |

**Table 9** Summary of pulmonary manifestations post-SCT (CengizSeval et al. 2018)

| Entity | Onset | Clinical manifestations | Steroid response | Prognosis |
|--------|-------|------------------------|------------------|-----------|
| **PERDS** | Acute | Within 96 hours of neutrophil recovery, in auto-HSCT recipients, diffuse lung infiltrates, with erythematous maculopapular rash, and no infection | Good | Good |
| **IPS** | Subacute | Allo-SCT recipients, with progressive respiratory failure, no infection, lung biopsy shows diffuse alveolar damage or interstitial pneumonitis | Poor | Poor |
| **DAH** | Acute | Hemoptysis, diffuse pulmonary infiltrates, BAL shows bloody aspirate with >20% hemosiderin-laden macrophages in BAL fluid, absence of infections | Poor | Poor |
| **DPTS** | Subacute | Auto-SCT recipients, after conditioning regimens containing BCNU, with exertional dyspnea, PFT s/o reduced DLCO | Good | Good |
| **PCT** | Subacute | Pediatric patient with GVHD, fever + peripheral pulmonary nodules on chest CT, biopsy s/o necrotic, basophilic thrombus with entrapped monocytes | n/a | Good |
The incidence varies from 1.6% to 7.2% (Carreras et al. 2019). Two retrospective Indian studies in pediatric patients have described its incidence to be 8.4% and 17%, respectively (Kapoor et al. 2018; Doval et al. 2019). In contrast to its name, it is not always reversible. If not recognized early, it can lead to permanent neurodeficits, as a result of status epilepticus, intracranial bleed, or ischemic infarcts (Schmidt et al. 2016). Many factors predispose to development of PRES in any patient. Underlying disorders (hemoglobinopathies especially sickle cell > thalassemia) (Schmidt et al. 2016; Gaziev et al. 2017), hematological malignancies (Allo-SCT for myeloma) (Bartynski et al. 2005), conditioning (MAC, TBI-containing regimens), unrelated donor transplant (Schmidt et al. 2016), presence of concomitant acute GVHD/steroid therapy, and CNI as GVHD prophylaxis (Bhunia et al. 2019). Typical clinical features include headache with a surge in blood pressure, visual disturbance, seizures, focal neurodeficit with possible renal dysfunction. Although vasogenic edema may be seen in CT in some patients, MRI is more sensitive. T2w-MRI sequences show bilateral multifocal areas of hyperintensity in white matter of parieto-occipital regions. This MRI feature has to be differentiated from acute toxic encephalopathy, which has similar changes. Whereas subcortical white matter is involved in PRES, periventricular white matter is predominantly affected in acute toxic encephalopathy. (Carreras et al. 2019). Hence, MRI with FLAIR sequence is the imaging modality of choice in all patients suspected of having PRES (Kapoor et al. 2018).

Management

1. Discontinuation of CNIs (Calcineurin inhibitors).

   There is enough evidence to show that CNI-induced PRES need not always have supratherapeutic levels. Hence, irrespective of drug levels, CNI should be discontinued (Schmidt et al. 2016). It has been shown that after discontinuation of CNI, neurological symptoms resolve within 3–8 days. However, the possibility of worsening/leading to de novo GVHD, after CNI discontinuation is an unsolved issue. Unfortunately, there are no guidelines for the same (Gaziev et al. 2017). Majority of experts recommend shifting to MMF ± Steroids for GVHD prophylaxis. However, there is evidence to say that this is inadequate, and shifting to mTOR inhibitors (Everolimus, Sirolimus) as a CNI-free GVHD prophylaxis would be better (Schmidt et al. 2016; Schleuning et al. 2009). As per Schmidt et al., switching to Everolimus was well tolerated, without any seizures/hypertension, with survival similar to that of patients without PRES (Schmidt et al. 2016). Substituting with an alternate CNI, or restarting same CNI after resolution of symptoms, has shown to lead to recurrence of seizures (Gaziev et al. 2017).

2. Antihypertensives.

   For BP control, in the first 2 hours, not >20–25% reduction should be attempted, as overzealous faster correction could hamper cerebral perfusion. IV Labetolol and IV sodium nitroprusside are two easily available parenteral medications. Other medications include Nicardipine and Fenoldopam. Labetolol has been found to be safe and effective (Kapoor et al. 2018). Clinical resolution has been shown in 2–5 days of blood pressure control (Schmidt et al. 2016). Resolution of MRI features take 2–4 weeks.

3. Antiepileptics.

   Antiseizure medications have to be started as per institution policy. Although any of the following – fosphenytoin, phenobarbitone, levetiracetam – can be given, latter (levetiracetam) is preferred due to relative paucity of drug interactions (Schmidt et al. 2016; Kapoor et al. 2018). Oral valproate has been proven to be ineffective in prevention of seizures (Gaziev et al. 2017).

4. Complement inhibition.

   Similar to its role in TA-TMA, Eculizumab has been shown to be useful in patients with PRES, refractory to conventional therapies (Bhunia et al. 2019).
**Prognosis**

Gaziev et al. showed that patients with PRES had significantly lower survival, as compared to patients without PRES. This difference was highly detrimental to the cohort of patients with sickle-cell disease (Gaziev et al. 2017). On the other hand, studies have shown no difference in survival, irrespective of PRES (especially when Everolimus-based regimen was used as GVHD prophylaxis) (Schmidt et al. 2016), including a recent publication on haplo-SCT patients (Chen et al. 2020). It is important to recognize that permanent neurodeficits can occur in 12% patients of PRES, if not recognized early (Burnett et al. 2010).

**Graft Failure**

Graft failure and poor graft function are related, but very important terms, in the field of transplant. As per definition, after SCT, **Engraftment** is coined when recipient achieves an absolute neutrophil count > 500 cells/liter [(ANC) > 0.5 × 10^9/L], on the first day of three consecutive days. Similarly, platelet recovery is defined as a platelet count >20,000 cells/liter [(PLT) > 20 × 10^9/L] on the first day of seven consecutive days without transfusion support. Primary graft failure is characterized by nonachievement of engraftment [peripheral blood ANC < 0.5 × 10^9/L by day +28 after allo-HSCT, in the absence of relapse] and absence of initial donor cell chimerism (donor cells <95%). For umbilical cord blood transplant, the cut-off is relaxed to day+42 for the same definition. In contrast, secondary graft failure is characterized by loss of donor cells after initial engraftment and recurrent ANC < 0.5 × 10^9/L. On the other hand, poor graft function is defined as at least two severe cytopenias ± transfusion dependency in the presence of a hypoplastic/aplastic bone marrow, in absence of severe GVHD/relapse, **with full donor chimerism**. While incidence of graft failure ranges between 3.8% and 5.6%, poor graft function ranges from 5% to 27%. It is imperative to remember that graft failure rates vary as per transplant settings (Ozdemir and CivrizBozdağ 2018) (Fig. 6). Similar to graft failure, is another term called ‘Graft Rejection’, which is an immune mediated rejection of donor cells by the host. However, the prognosis of primary and secondary graft failure is dismal, with 5-year OS <20% (Carreras et al. 2019) (Tables 10 and 11).

**DSA (Donor-Specific Antibodies)**

Donor-specific antibodies are preformed/pre-existing donor-specific anti-HLA antibodies in the recipient. They occur due to previous transfusions, or prior pregnancy, and increase the risk of graft failure two–tenfold, irrespective of the stem cell source and conditioning regimen. The specificity of these DSAs is important. Those against class I (HLA-A, and HLA-B) and class II (HLA-DRB1) are detrimental versus those antibodies against HLA-DPB1 and HLA-DQB1, which have an uncertain role (Brand et al. 2013). The overall prevalence of DSAs in haploidentical HSCT is 10–20%. The frequency is higher in multiparous females and patients who have received may allogeneic blood products. In general, antibody-mediated graft failure is due to either ADCC (antibody-mediated cellular cytotoxicity) or CDC (complement-dependent cytotoxicity) (Ciurea et al. 2018).

It is imperative for the transplant physician to detect these DSAs prior to transplant. The methods used for detecting these DSAs are either cell-based assays or solid-phase immunoassays. In cell-based cross-matched assays, donor WBCs are incubated with recipient serum. If patient’s serum contains DSA, antibody will be its corresponding target antigen on donor lymphocytes, and give a positive result. Problems associated with this test include need for greater number of viable donor lymphocytes, detection of non-HLA antibodies (clinical relevance questionable), and its inability to find out specificity of antibodies. On the other hand, solid-phase immunoassays (SPI) utilize solid matrix-bound solubilized HLA molecules, against the patient’s serum, to detect a reaction. This solid matrix can be either microtiter plate (enzyme-linked immunosorbent
Evaluation of cytopenias post-transplant
Do a marrow to rule out a relapse
Look at marrow cellularity – hypocellular marrow

Look at Donor chimerism

Mixed / full recipient chimerism
Donor chimerism 95-100%

Graft failure
Poor graft function

Look for previous evidence of engraftment
Look for evidence of previous hematologic recovery.
If No – primary, otherwise – secondary

Primary graft failure
Secondary graft failure

Fig. 6 Algorithm for diagnosis of graft failure and poor graft function. (Adapted from Ozdemir and CivrizBozdağ 2018)

Table 10 Risk factors for graft failure post-SCT (Carreras et al. 2019; Ozdemir and CivrizBozdağ 2018)

| Pretransplant (unmodifiable) | Pretransplant (modifiable) | At/Posttransplant |
|-----------------------------|---------------------------|-------------------|
| Donor related               | Graft source (cord blood > bone marrow > peripheral blood) | Low CD34+ dose |
| HLA mismatch                | T-cell depleted graft     | Drug toxicity     |
| Donor age                   |                           |                   |
| Female donor to male recipient |                         |                   |
| Recipient related           | Conditioning chemotherapy [RIC > MAC, Conditioning including Bu-cy, TBI protective in unrelated donor/ 4/6 CBT] | Viral infections |
| Nonmalignant disease        |                           | GVHD              |
| Myelofibrosis               |                           |                   |
| Advanced disease            |                           |                   |
| Splenomegaly                |                           |                   |
| Iron overload               |                           |                   |
| Previous blood transfusions/pregnancy |                 |                   |
| Age < 30 years              |                           |                   |
| Anti-HLA antibodies (DSA in haplo-HSCT) | |                   |

[refer description below]
assay; ELISA) or polystyrene beads (multiplexed multianalyte bead arrays) performed on a conventional flow cytometer or a fluoroanalyzer (Luminex). The Luminex SAB (single antigen bead) array enables us to detect antibodies with HLA specificity. The latter are more sensitive, as they can detect even low-level anti-HLA antibodies in patient’s serum. SPIs are now preferred for detection and monitoring of DSA in HSCT. In case the patient is found to be positive on SPI, further modified techniques like C4d or C1q are done to detect complement-fixing antibodies, which are associated with poor graft survival. A positive test for DSA is considered when MFI (mean fluorescence intensity) is \( > 1000 \). Importantly, although rejection can occur at any level beyond 1000 MFI, \( > 5000 \) MFI are associated with high levels of primary graft failure (Ciurea et al. 2018).

## Management of Graft Failure

### Prevention

- Identify DSA. Desensitize if \( > 1000 \) MFI.
- Consider use of peripheral blood as stem cell source.
- Include low dose TBI and/or ATG in the conditioning regimen.
- G-CSF use posttransplant.
- Close evaluation of engraftment [including marrow chimerism studies shortly after transplant (day +14)] (Carreras et al. 2019).

### Treatment

1. Stop all nonessential myelotoxic drugs (Linezolid, Ganciclovir, Acyclovir). Address and treat infections, in any and rule out any evidence of disease relapse (Carreras et al. 2019; Ozdemir and CivrizBozdağ 2018).

2. **Administer growth factors.**
   a. G-CSF: Bittencourt et al., in their retrospective study, showed that 95% patients responded to administration of G-CSF. Of these, nearly three-fourth responses were well-sustained even after G-CSF discontinuation. Importantly, they showed that patients whose WBC count increased to \( > 0.1 \times 10^9/L \) within 3 days of G-CSF support were more likely to have a sustained response (Bittencourt et al. 2005).

## Management of DSA Positive Recipients

There is no specific standard of care for DSA positive recipients. The same concepts and drugs are used in various combinations.

a. **Antibody removal:** by Plasmapheresis (most common desensitization method). It is done for 1–4 procedure days between days 10 and 17, and even posttransplant.

b. **Inhibition of antibody production:** Rituximab 375 mg/m² or Bortezomib (proteasome inhibitor) prior to conditioning.

c. **Antibody neutralization:** IVIg donor platelets or “buffy coat” (white blood cells) infusion.

d. **Avoid complement activation:** IVIg, complement blockade (Eculizumab) (Carreras et al. 2019).

### Table 11 Minimum and optimal amount of cells (TNC/CD34) in transplants (Carreras et al. 2019)

|                | Minimum                  | Optimal                  |
|----------------|--------------------------|--------------------------|
| Bone marrow    | Autologous Allogeneic    | TNC: 2 \( \times 10^6/kg \) TNC: 3 \( \times 10^6/kg \) |
| Peripheral blood| Autologous Allogeneic    | CD34: \( > 1 \times 10^6/kg \) CD34: \( > 2 \times 10^6/kg \) |
| Cord blood     | HLA 4–6/6                | TNC: \( >2.5–3 \times 10^6/kg \) CD34: \( >1 \times 10^6/kg \) |
b. rh-EPO: Jaspers et al., in their prospective study, showed that administration of rh-EPO at 500 U/kg weekly in the first month after Allo-SCT, decreased transfusion needs (Jaspers et al. 2014). However, there was no significant benefit in long-term survival after Allo-SCT (Jaspers et al. 2015).

c. TPO-RAs (Thrombopoietin receptor agonists): Eltrombopag is a small molecule TPO-RA used in ITP (Immune thrombocytopenia) and Aplastic anemia. It has been used in patients with absence of platelet engraftment and in those with poor graft function, with 60–70% response rates (Carreras et al. 2019; Ozdemir and CivrizBozdağ 2018; Yuan et al. 2019).

3. Posttransplant immunosuppression – Maintain adequate levels of immunosuppression in post-transplant period. If there is presence of mixed chimerism after a RIC transplant, rapid tapering of adequate immunosuppression is beneficial (Carreras et al. 2019).

4. DLI (Donor Lymphocyte Infusion) and CD34 Boost – DLI could be recommended if decreasing levels of donor chimerism are observed. On the other hand, CD34 boost without prior conditioning can be given for patients with poor graft function, i.e., persistent for 2 months after its onset (Carreras et al. 2019).

5. Second Allo-HSCT

The outcome of a patient with graft failure is dismal. Hence, second transplant remains the only option at times, in conditions of despair. Regarding donor choice, unless there is significant delay, different donor should be chosen. Haploidentical donors can be considered. Conditioning before second transplant is required. Ferra et al. showed in their study that Fludarabine/ATG (antithymocyte globulin) and Cyclophosphamide/ATG conditioning regimens with a high CD34 dose could achieve engraftment with low toxicity. Peripheral blood is the preferred graft, with posttransplant immunosuppression with calcineurin inhibitor-based regimens. Ex-vivo T-cell depletion should be avoided, especially if there was previous immune graft rejection (Carreras et al. 2019).

Mucositis

Mucositis refers to mucosal damage secondary to chemotherapy. It can occur in the oral cavity; pharyngeal, laryngeal, esophageal regions; and other areas of the gastrointestinal tract. Mucositis occurs in approximately 20–40% of patients receiving conventional chemotherapy, but its frequency is up to 80% in patients receiving high-dose chemotherapy as conditioning for HSCT (Lalla et al. 2014). All patients undergoing myeloablative conditioning, methotrexate based GVHD prophylaxis, prior radiotherapy of head-neck region, are at high risk of development of mucositis. Symptoms of mouth and throat pain typically begin within 7–10 days, after the start of conditioning regimen. This may persist for 2–3 weeks. Importantly, mucositis typically affects nonkeratinized portions of buccal and labial mucosa, latero-ventral surface of tongue, and soft palate. Lesions begin as erythema followed by well-defined smooth membranes. When ulcerations affect keratinized surfaces (gingiva, tongue dorsum, hard palate), it is most likely due to HSV reactivation (Treister 2013). The pathobiology of mucositis includes direct damage from chemotherapy/radiotherapy, reactive oxygen species, pro-inflammatory cytokines, and metabolic byproducts of colonizing microorganisms. Mucositis leads to a significant financial impact, including possibility of secondary infection, nutrition support, analgesia, and hospital stay (Lalla et al. 2014).

Patients should be evaluated daily for oral pain, and examined for mucosal changes. There are multiple severity assessment scales (Table 12) to guide management (Treister 2013).

Management

At the earliest indication of oral symptoms, the patient should be given a soft, bland diet to prevent irritation and injury to oral mucosa. If it progresses, patients may need a liquid diet with or without supplemental IV nutrition. In severe cases, one may need TPN (Total parenteral nutrition). Patients should be instructed to keep oral cavity clean and free from any secondary
Topical analgesics (swish and spit) can help control symptoms. These include viscous lidocaine, “magic mouth wash” (equal portions of lidocaine, diphenhydramine, Maalox), and morphine solution. Some patients may need opioids for pain relief (Treister 2013). Patient-controlled analgesia with morphine or transdermal fentanyl patch can be used to treat pain due to mucositis (Lalla et al. 2014).

MASCC-ISOO (Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology) recommends oral cryotherapy, palifermin (human keratinocyte growth factor-1), low-level laser therapy, and benzydamine mouth wash, as measures to prevent mucositis. Among these, palifermin and laser therapy are the two modalities used in the field of HSCT. Palifermin is the only FDA approved agent for mucositis prevention. It is given at a dose of 60 μg/kg/day for 3 days prior to conditioning and 3 days after transplant, in patients receiving TBI-based conditioning in context of an autologous HSCT. On the other hand, low-level laser therapy (wavelength 650 nm, power 40 mW, and each square centimeter treated with required time to a tissue energy dose of 2 J/cm²) can be used, irrespective of whether TBI was used in conditioning or not. Oral cryotherapy would be of benefit to patients receiving high-dose melphalan, with or without TBI for conditioning. On the other hand, panel recommended against the use of sucralfate mouth wash, chlorhexidine mouthwash, systemic pilocarpine for prevention (Lalla et al. 2014). Caphosol, a neutral, supersaturated, Ca(2+)/PO(4)(3-) mouth rinse, has been shown to reduce the severity of mucositis, duration of analgesia, and days to engraftment (Papas et al. 2003). The same was reiterated by Quinn (2013), when he reviewed the data from 24 studies (Quinn 2013).

### Recent Trends in Mucositis

A pharmacokinetic–pharmacodynamic study from India showed that Curcumin decreased the levels of inflammatory cytokines in patients receiving high dose melphalan for ASCT. This could be further explored in the clinical setting (Khattry et al. 2012). Similarly, a second study from the same center explored the combination of resveratrol-copper 48 hours prior till 21 days after melphalan infusion. They showed that it reduced the levels of serum IFNγ and salivary IL-1β, TNF-α with a significant reduction of oral mucositis (Agarwal et al. 2020). Another study from India observed that supersaturated calcium phosphate was ineffective for prevention and treatment of mucositis (Bhatt et al. 2017). To reiterate the above finding, as per recent abstract at European Hematology Association 2020, a randomized trial between cryotherapy and supersaturated calcium phosphate did not find any difference between the two for prevention of oral mucositis (Belloumi et al. 2020).

### Conclusion

A broad spectrum of acute complications post-transplant contributes to morbidity and mortality. It is imperative that transplant physicians are cognizant of these syndromes for early diagnosis and
apt intervention. Research is required to better elucidate their biology in order to find more definitive therapies.

Cross-References

- Biology of Graft-Versus-Host Disease
- Cellular Therapy
- HLA in Hematopoietic Stem Cell Transplantation
- HSCT in Benign Hematological Disorders
- HSCT in Malignancies
- Immunosuppressive Therapy and Immunomodulation in Stem Cell Transplantation
- Pediatric Bone Marrow Transplantation
- Transplant Pharmacology and Conditioning Therapy

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