

* CHAPTER 9

Early complications after HSCT

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1. Introduction

The high dose of RT and/or CT included in conditioning regimens (see Chapter 6) affects all organs and tissues of the recipient, producing several early and late secondary effects of variable intensity. The most common early effects like nausea, vomiting, mucositis and pain are treated in Chapter 8, and late effects are covered in Chapter 12. In this Chapter we summarise some early complications that, despite not being very frequent, are an important cause of morbidity and mortality.

2. Haemorrhagic cystitis (HC) (1)

Pathogenesis

HC is produced by direct toxicity of the conditioning regimen on the urothelium or by viral infections affecting the urinary tract. Usually, HC secondary to conditioning appears early after HSCT (several days after receiving CT agents) and can be produced by Cy (or ifosfamide), Bu (especially if combined with Cy), VP or TBI (both uncommon). Viral HC appears later (usually after day +30) and can be due to human polyomavirus type BK or JC, adenovirus type 11 (less frequent) or CMV (exceptional).

Incidence

HC secondary to CT: 1 to 25%, depending on the preventive measures adopted. The incidence of viral HC is not well established; 5 to 25%, according to the degree of immunosuppression of the recipient.

Prophylaxis

Continuous irrigation of the bladder during conditioning is effective but is no longer used. Nowadays, HC prophylaxis is based on hyperhydration and Mesna administration. The recommended daily dose of hydration is 3 L/m². The usual daily dose of Mesna is 1.0–1.5 x daily dose of Cy (e.g. daily dose of Cy: 4.2 g → daily dose of Mesna: 4.2–6.3 g) administered IV as: a) continuous infusion in 1 L of 0.9% saline over 12–24 hrs, beginning 4 hours prior to the 1st dose of Cy and ending 12–24 hrs after the last Cy dose; or b) bolus injections, 20% of daily dose of Cy dose administered as a bolus 1/2–1 h before Cy and the remaining daily dose divided into bolus injections q 2–3 h, maintained up to 12–24 after ending Cy. Despite these classical forms of administration, some pharmacodynamic studies have shown that the best method of administering Mesna is to combine a continuous infusion with intermittent bolus injections during the 6 hrs after Cy dose. The presence of acrolein in the bladder 24 h after Cy makes it advisable to prolong Mesna administration 24 hrs after the last Cy dose.

Treatment

Treatment should be based on a three step approach:

1. Forced hydration plus intensive platelet support. The use of procoagulant agents

like aminocaproic acid is contraindicated because they favour clot formation in the bladder.

2. Continuous bladder irrigation with saline solution. Some success has been reported with bladder instillation of alumina 1% (risk of encephalopathy if associated renal failure), prostaglandin E2 or E1, GM-CSF or cidofovir (all with limited experience). Similarly, hyperbaric oxygen or oestrogens (2–4 mg q 8 h p.o., Odermann et al., BMT 2000) have also been reported as effective measures.
3. If the previous measures do not solve HC other salvage approaches can be considered: selective embolisation of bladder arteries (one of the simplest and effective measure in the hands of an expert angiologist) (2); suprapubic cystotomy; cystoscopy + installation of formalin (very painful, risk of scars and bladder contraction, requires anaesthesia); catheterisation of both ureters to rest the bladder; hypogastric bond (can produce sexual impotence); and, as a last resort, cystectomy.

3. Early complications of vascular origin

Injury of the vascular endothelium seems to be the most important initial event in a variety of complications with imprecise diagnostic criteria and overlapping clinical features, which are observed within the first 30–60 days after HSCT. The best defined syndromes resulting from this endothelial injury are: 1) Veno-occlusive disease of the liver; 2) Capillary leak syndrome; 3) Engraftment syndrome; 4) Diffuse alveolar haemorrhage; 5) Thrombotic microangiopathy; 6) Idiopathic pneumonia syndrome; 7) Multiple-organ dysfunction syndrome. [Figure 1](#) shows their common pathogenesis.

3.1. Hepatic veno-occlusive disease (VOD)

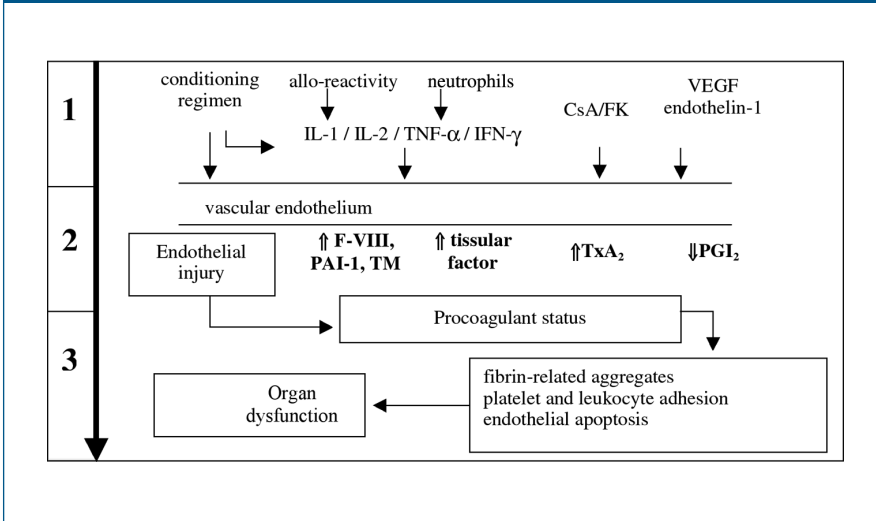
Definition

VOD is the term used to designate the symptoms and signs that appear early after HSCT as a consequence of the conditioning regimen-related hepatic toxicity. This syndrome is characterised by jaundice, fluid retention and tender hepatomegaly appearing in the first 35–40 days after HSCT (3–8).

Pathogenesis (3, 6–8)

The hepatic metabolism of certain drugs (e.g. Cy) by the cytochrome P-450 enzymatic system produces several toxic metabolites (e.g. acrolein). These toxic metabolites are converted to stable (non-toxic) metabolites by the glutathione enzymatic system (GSH) and eliminated. When this process occurs in patients with a reduced GSH activity, due either to pre-existing liver disease or to the action of agents as Bu, BCNU or TBI that reduce GSH levels, toxic metabolites are not

Figure 1: Common pathogenesis of early complications of vascular origin after HSCT



VEGF: vascular endothelial growth factor; Tx: thromboxane; PG: prostaglandin; TM: thrombomodulin; PAI-1: plasminogen activator inhibitor type 1

metabolised. Toxic metabolites are predominantly located in area 3 of the acinus (around centrilobular veins) because this area is rich in P-450 and poor in glutathione. Consequently, damage to hepatocytes and sinusoidal endothelium occurs predominantly in this anatomic zone. The remaining factors mentioned in Figure 1 can also contribute to the endothelial injury.

Experimental models show that the first events after endothelial injury by toxic metabolites are loss of sinusoidal endothelial cell (SEC) fenestrae, formation of gaps within and between SEC, and rounding up or swelling of SEC. Consequently, red blood cells penetrate into space of Disse and dissect off the sinusoidal lining, which embolises downstream and blocks the sinusoids reducing the hepatic venous outflow and producing post-sinusoidal hypertension. In the light of all these observations some authors have proposed the term of sinusoidal obstruction syndrome (SOS) for this complication.

Clinical features (3, 4, 6, 8)

Classical VOD. Occurs within days after conditioning (from day -1 to +14) and is characterised by presence of: jaundice (in almost 100% of cases), hepatomegaly and/or

right upper quadrant pain, and weight gain (not attributable to excessive fluid administration) with oedemas and ascites.

Late VOD. The same clinical manifestations as classical VOD but developing late after HSCT (one third of cases occur after patient discharge). Mainly observed after conditioning including several alkylating agents in combination (busulfan, melphalan, thiotepa). One third have a biphasic course with an initial transitory peak followed by a definitive late phase (5)

VOD with multiorgan failure. The same clinical manifestations as previously described plus: thrombocytopenia (refractoriness to platelet transfusions); pleural effusion / pulmonary infiltrates; progressive renal, cardiac, pulmonary failure; confusion, encephalopathy and coma.

Incidence

The incidence of VOD ranges from 3 to 54% in the largest series. This variability is the consequence of the presence or absence of a number of well-known risk factors for this complication (see [Table 1](#)). In the only prospective multicentre study published the incidence of VOD was 8% in allo-HSCT and 3% in auto-HSCT (6).

Diagnostic criteria

As for any syndrome the diagnosis of VOD must be established clinically. All HSCT teams use one of the following sets of clinical criteria (3, 4, 6, 8):

Seattle criteria: In the first 20 days after HSCT presence of two or more of the following: bilirubin > 2 mg/dL; hepatomegaly or pain in the right-upper quadrant; weight gain (>2% basal weight).

Baltimore criteria: In first 21 days after HSCT, presence of bilirubin >2 mg/dL plus ≥ 2 of the following: painful hepatomegaly; ascites; weight gain (>5% basal weight). In both, other possible causes of these clinical features should be excluded before accepting the diagnosis of VOD (see differential diagnosis). Additionally, it is necessary to remember that some VOD cases can appear late after HSCT.

Additional investigations

Other complementary studies that can aid diagnosis are:

Haemodynamic study of the liver carried out through the jugular or femoral veins (9): Despite its usefulness, this is only indicated to confirm the diagnosis of VOD before adopting a therapeutic approach that may be potentially hazardous for the patient. An hepatic venous gradient pressure (HVGP) ≥ 10 mmHg in a patient without previous liver disease allows a precise differential diagnosis with a high degree of specificity. However, a normal HVGP does not exclude the diagnosis of VOD.

Liver biopsy: Thrombocytopenia usually present in this phase of HSCT precludes a transperietal liver biopsy; consequently hepatic tissue can only be obtained by means of a transvenous biopsy in the course of a haemodynamic study. In addition to the

Table 1: Risk factors (3, 4, 6–8)

Risk	Lower risk < Higher risk
Transplant type	Syngeneic or autologous < allogeneic
Donor type	Sibling < another relative < unrelated
HLA compatibility	HLA match < any mismatch
Stem cell origin	Peripheral blood < bone marrow
T-cell depletion	With TCD < without TCD
Diagnosis	non malignant disease < malignant disease
Status of the disease	Remission < relapse
Conditioning	
- Intensity	Cy alone < Cy + TBI < BVC (a)
- TBI	Fractionated TBI < single dose TBI
	Less than 12 Gy < more than 12 Gy
	Low dose rate < high dose rate
- Busulfan	IV BU < adjusted oral Bu < non adjusted oral Bu
- Timing	Interval Cy – TBI 36 hours < 12 hours
Age / Sex	Younger < older / men < women
Karnofsky index	100–90 < lower than 90
ASAT/ALAT before HSCT	Normal < high
Transplant number	First < second
Previous hepatic irradiation	No < yes
Previous Mylotarg	No < yes (b)
Status of the liver	Normal < fibrosis < cirrhosis or infiltration
CMV serological status	Negative < positive
Fever in conditioning	Absent < present
Hepatotoxic drugs	Progestogens, ketoconazole, CsA, methotrexate, amphotericin B, vancomycin, acyclovir, IV Ig (c)
Genetic predisposition	GSTM1 positive < GSTM1 null genotype (d)

The most important risk factors are indicated in bold type. (a) BVC (BCNU, VP, Cy). (b) VOD incidence up to 64% (Wadleigh et al. Blood 2003). (c) Higher incidence of VOD with high-dose IVIg. (d) Srivastava et al., Blood 2004

classical histological changes of VOD (concentric non-thrombotic narrowing of the lumen of small intrahepatic veins) other less specific abnormalities can be observed in patients with a VOD syndrome, including eccentric narrowing of the venular lumen; phlebosclerosis; sinusoidal fibrosis and hepatocyte necrosis. Due to patchy nature of VOD a normal biopsy does not exclude the diagnosis.

Ultrasound: A variety of abnormalities can be observed; gallbladder wall thickening, ascites, hepatomegaly and attenuate or reversed portal flow, but all of them are non-specific.

Biological markers: Although the serum of patients with VOD shows an increase in

levels of plasminogen activator inhibitor-1 (PAI-1) (marker with the highest specificity and sensitivity for VOD), aminopropeptides of type III collagen, and hyaluronic acid, all these measurements are of little utility in routine clinical practice.

Differential diagnosis

To accept the diagnosis of VOD all the following possible causes of similar clinical features should be excluded as far as possible, including:

- Infections: *Cholangitis lenta* (sepsis of liver) / fungal infection / viral hepatitis
- Immune dysfunctions: Acute GvHD of the liver
- Drug toxicity: CsA, azoles, MTX, progestogens, trimethoprim-sulphamethoxazole, TPN, among others
- Reduction of venous outflow / increased volume: Constrictive pericarditis / congestive heart failure / fluid overload / renal failure
- Others: Pancreatic ascites / chylous ascites / infiltration of the liver.

Prophylaxis of VOD (6, 8) (Table 2)

Table 2: Prophylaxis of VOD

Avoidance of risk factors

- When possible delay HSCT if an acute hepatitis exists; adjust Bu dose or use IV Bu; fractionate TBI; avoid hepatotoxic drugs, etc.
- In high risk patients, consider allo-RIC HSCT (lower incidence of VOD)

Pharmacological

The following drugs have been used to prevent VOD from the beginning of conditioning until day +21–30:

- Sodium heparin: 100 U/kg/day by continuous infusion. Two randomised studies showed a beneficial effect but others have suggested that it is ineffective and dangerous
- Prostaglandin E1: 0.3 µg/kg/h by continuous infusion. Evaluated in several clinical trials usually combined with heparin. When administered alone no beneficial effect was observed
- Ursodeoxycholic acid: 600–900 mg/day *p.o.* Four randomised trials and 2 historically controlled studies have shown a reduction in incidence of VOD and in TRM
- N-acetylcysteine. Very limited experience
- Low molecular weight heparin: Enoxaparin 40 mg/day or fraxiparin 5000 U/day subcutaneously seem to be relatively safe and may have some effect but a large randomised study is needed to confirm these results
- Pre-emptive ATIII replacement: Ineffective
- Defibrotide. Several preliminary reports have shown encouraging results

Treatment of established VOD (6, 8) (Table 3)

Table 3: Treatment of established VOD	
First line therapy	
Symptomatic (a)	<ul style="list-style-type: none"> - Restriction of salt and water intake ± diuretics - Maintain intravascular volume and renal perfusion by means of albumin, plasma expanders and transfusions (haematocrit >30%)
Specific (b)	<ul style="list-style-type: none"> - Defibrotide 6.25 mg/kg IV in 2 h infusion q 6 h IV during 14 days (1) (c) (d) - rt-PA 0.05 mg/kg/h during 4 hours (maximum 10 mg/day) for 2–4 days ± sodium heparin 20 U/kg as a bolus (maximum 1000 U) followed by 150 U/kg/day by continuous infusion for 10 days (e)
Other measures	
Symptomatic (a)	<ul style="list-style-type: none"> - Low dose dopamine (effectiveness not demonstrated) - Analgesia - Paracentesis / thoracocentesis - Haemodialysis / haemofiltration - Mechanical ventilation
Specific	<ul style="list-style-type: none"> - TIPS (transvenous intrahepatic portosystemic shunt) (f) - Surgical shunt - Liver transplantation

rt-PA: recombinant tissue plasminogen activator.

(a) Symptomatic treatment should be established first, reserving specific measures for most severe cases.

(b) Although other agents have been used (antithrombin III, prostaglandin, corticosteroids, glutamine/vitamin E, N-acetylcysteine, etc.) the only ones occasionally effective are those mentioned.

(c) Defibrotide permits the resolution of 50–55% of severe VOD with multiorgan dysfunction and a 47–60% of survival at day +100 with no secondary effects in adults and children (8, 10).

(d) In a randomised study defibrotide at 25 mg/kg/day has shown similar effectiveness to the classical dose of 40 mg/kg/d (8).

(e) rt-PA has been shown to be effective only in patients with a non-advanced VOD. Its use is contraindicated in patients with multi-organ dysfunction syndrome (MODS), haemorrhages or severe hypertension.

(f) Despite improvement in portal hypertension and ascites, long term efficacy and survival are extremely poor

VOD evolution (3, 4, 6 ,7) (Table 4)**Table 4: VOD evolution**

	Classification (a)	Frequency (b)
Complete resolution on day +100 w/o treatment	Mild VOD	8–23%
Complete resolution on day +100 with treatment	Moderate VOD	48–64%
Non resolution before death (c) or on day +100	Severe VOD (d)	23–28%
Mortality attributable to VOD by day +100 (e)		1–3% of all HSCT 18–28% of all VOD 75–95% of severe VOD (f)

(a) Classification described by Seattle group for retrospective evaluation of VOD. (b) Values observed in two large series (3, 6); (c) In many cases VOD is not the direct cause of death but contributes to it. (d) The severity of VOD can be predicted by means of a mathematical model (Bearman et al., JCO 1993). (e) Data from pre-defibrotide era. (f) The equivalent predicted mortality in non-severe VOD cases ranges between 10 and 20%

3.2. Capillary leak syndrome (CLS) (11)**Pathogenesis**

The injury to the capillary endothelium produces a loss of intravascular fluids into interstitial spaces and the clinical manifestations.

Incidence

The absence of well-established clinical criteria for its diagnosis precludes an accurate estimation of its incidence. Additionally, the differential diagnosis with VOD, ES or IPS can be very difficult.

Clinical features

Development, in the first 15 days after HSCT, of:

- Weight gain (>3% in 24 hours), and
- Generalised oedemas (ascites, pleural effusion, pericarditis) that characteristically does not respond to frusemide treatment.

Other features occasionally observed are: tachycardia, hypotension, renal insufficiency of pre-renal origin and hypoalbuminaemia.

Differential diagnosis

From engraftment syndrome (ES): Its earlier development, the absence of skin rash and the poor response to corticosteroids.

From VOD: The absence of jaundice and painful hepatomegaly, and the poor response to furosemide.

From IPS: The presence of generalised oedema.

Risk factors

The use of G-CSG, GM-CSF or K-CSF; high cumulative dose of CT in the pre-HSCT phase;

unrelated or HLA mismatched donor grafts.

Treatment

To withdraw growth factors. Despite being systematically used the response to corticosteroids is poor. There is no other specific treatment.

Evolution

There is a high mortality if it progresses to MODS.

3.3. Engraftment syndrome (ES) (12–14)

Pathogenesis

Massive release of pro-inflammatory cytokines by tissues injured by intensive conditioning and by recovering neutrophils has been hypothesised to play a role.

Incidence

Variable depending on the diagnostic criteria used. After auto-HSCT: from 5 to up to 25% in patients with breast cancer or autoimmune diseases. After conventional allo-HSCT: only occasionally described (possibly because of the difficult differential diagnosis from GvHD). After allo-RIC: 10% in a recent series (14).

Clinical features

Development, within 72 hours of the start of neutrophil recovery, of the following major clinical criteria:

- High fever of a non-infectious origin (unresponsive to antibiotics and negative cultures);
- Skin rash affecting >25% body surface and not attributable to an allergic reaction;
- Lung infiltrates or hypoxia not attributable to fluid overload, lung embolism, or congestive heart failure.

Other symptoms occasionally observed are diarrhoea, weight gain and liver, kidney or CNS dysfunction (minor criteria).

Diagnosis

There are no well-established criteria for its diagnosis. Spitzer (12): 3 major criteria or 2 major and one or more minor criteria; Majolino (13): fever with either skin rash, pulmonary infiltrates or diarrhoea; Gorack (14): ≥ 2 major criteria plus weight gain.

Risk factors

Most cases of ES have been described since the introduction of growth factors and use of PBSCT. For this reason, a high number of CD34+ cells, faster engraftment and use of growth factors (especially GM-CSF) are considered to be the main risk factors as well as the underlying disease (breast cancer, multiple sclerosis, POEMS syndrome).

Treatment

MethylPDN 1 mg/kg q 12 h (3 days) with progressive tapering over one week. An appropriate empiric antibiotic treatment should always be maintained due to the difficulty of excluding an infectious origin of the fever.

Evolution

Complete resolution in 1–5 days in >80% of cases if steroids are introduced early.

3.4. Diffuse alveolar haemorrhage (DAH) (15, 16)**Pathogenesis**

Very similar to VOD pathogenesis but affecting the lungs.

Incidence

The reported incidence ranges from 1 to 5% in auto-HSCT and from 3 to 7% in allo-HSCT. Some authors consider that underlying undetected infections can play a role in DAH pathogenesis and postulate that infection-associated alveolar haemorrhage and DAH should be considered as equivalents.

Clinical features

Despite some cases of late-onset DAH, it is usually diagnosed within the first 30 days after HSCT. The main manifestations are:

- Dyspnoea, non productive cough, tachypnoea
- Hypoxaemia that can require oxygen-therapy
- Chest X-ray or CT with focal or diffuse interstitial or alveolar infiltrates located in middle and inferior lung fields
- Bronchoalveolar lavage (BAL) progressively bloodier, and not attributable to infection (absence of pathogens in BAL), thrombocytopenia, fluid overload or heart failure. Successive aliquot of 20 mL, in at least three segmentary bronchi, become progressively more bloodstained (indicating blood in the alveoli).

Risk factors

DAH is not related to low platelet counts. Factors that favour this complication are older age, previous thoracic radiation, allogeneic donor, myeloablative conditioning, and severe acute GvHD.

Treatment

After publication of some small retrospective series high-dose methylPDN (250–500 mg q 6 h, 4–5 days and tapering in 2–4 weeks) was considered the treatment of choice. However, many other authors have not observed that corticosteroids modify the poor outcome associated with DAH. Recombinant FVIIa has been used with success in some cases. The possible role of cytokine antagonists and anti-inflammatory agents should be evaluated.

Evolution

The overall mortality rate at 60 days from the onset of the haemorrhage is around 75% despite in many patients the death is not directly related to the haemorrhage.

3.5. Thrombotic microangiopathy (TMA) (17–20)

TMA is the term used to describe haemolytic uraemic syndrome (HUS) and thrombotic

thrombocytopenic purpura (TTP) associated with HSCT.

Pathogenesis

Conditioning regimen related toxicity, together with other triggering factors that are not clearly understood, produces a generalised endothelial dysfunction with intravascular platelet activation and formation of platelet-rich thrombi within the microcirculation. In contrast to classical TTP, ADAMTS13 activity very rarely falls below 10%.

Incidence

Less than 4% in auto-HSCT. Up to 15% in allo-HSCT (7% in an EBMT survey).

Clinical manifestations

Usually develop around day +60 but early (day +4) and late (2 years) episodes have been described. Characterised by:

- Microangiopathic haemolytic anaemia (MHA) (anaemia, >2–5% schistocytes, LDH and other markers of haemolysis)
- Thrombocytopenia or increase in transfusional requirement
- Fever of non-infectious origin
- Renal dysfunction and/or neurological abnormalities (cortical blindness, seizures, typical images in CNS CT-scan).

Diagnostic criteria for HSCT-associated TMA (Table 5)

Table 5: Diagnostic criteria for HSCT-associated TMA

Blood & Marrow Transplant Clinical Trials Network consensus (18)

- 1) RBC fragmentation and 2 schistocytes per high-power field on PB smear
- 2) Concurrent increased serum LDH
- 3) Concurrent renal (a) and/or neurologic dysfunction w/o other explanations
- 4) Negative direct and indirect Coombs test

International Working Group (19)

- 1) Increased percentage (>4%) of schistocytes in the blood
- 2) *De novo*, prolonged or progressive thrombocytopenia
- 3) Sudden and persistent increase in LDH
- 4) Decrease in Hb concentration or increased RBC transfusion requirement
- 5) Decrease in serum haptoglobin concentration

(a) *Doubling of serum creatinine from baseline*

Risk factors

A higher incidence has been observed in patients receiving TBI, calcineurin inhibitors (CNI), sirolimus, unrelated or HLA-mismatched donor grafts, or developing GvHD or CMV/fungal infections.

Clinical forms

Two main forms of TMA can be observed:

1. CNI-associated nephrotoxicity (or neurotoxicity) with MHA: Classically develops early after HSCT, is related to toxic levels of CNI, and is reversible after stopping its administration. Usually has a favourable evolution if it improves quickly after stopping CNI.
2. Not associated with CNI toxicity, with two clinical forms:
 - a. Conditioning associated HUS: TMA primarily affecting the kidney, often causing oliguric or anuric renal failure with hypertension, MHA and thrombocytopenia, and
 - b. Fulminating multifactorial TMA: Early after HSCT, renal failure, CNS disturbances, hypertension, MHA and thrombocytopenia associated with GvHD, viral or fungal infection. Most cases have a fatal evolution and do not respond to CNI suppression, plasma exchange or other treatments (see below).

Prevention

The only reasonable measure is to have a close control (2–3 times per week) of CNI, LDH and creatinine levels. If any of them increase peripheral blood smear, haptoglobin and CNI metabolites should be tested.

Treatment

The only effective measure in some cases is to immediately stop CNI, adding another agent for GvHD prophylaxis/treatment (corticosteroids, mycophenolate, azathioprine). Plasma exchange cannot be currently considered the standard of care despite some success (less than 50% of responses and 70–90% of mortality in published series possibly due to selection bias). Some authors have reported successful results with anti-TNF MoAb (etanercept/infliximab), defibrotide, daclizumab, rituximab, and eicosapentaenoic acid.

3.6. Idiopathic pneumonia syndrome (IPS) (21)

Pathogenesis

The formerly used term of interstitial pneumonia has been progressively abandoned because it does not correspond to the real pathologic findings. Apparently, this syndrome is the result of a diversity of lung insults, including the toxic effects of conditioning, immunologic cell-mediated injury, inflammatory cytokines and, probably, occult pulmonary infections.

Incidence

As a consequence of the improvement of diagnostic methods the incidence of IPS has reduced from more than 20% in earlier series of allo-HSCT to less than 10% at present time (8.4 and 2.2% after conventional and allo-RIC, respectively, in a recent series). It is uncommon in auto-HSCT setting.

Clinical features

Development around day +21 of:

- Fever, non-productive cough
- Tachypnoea, hypoxaemia
- Diffuse alveolar or interstitial infiltrates on X-ray or scan.

Diagnosis

The diagnosis is confirmed when the previous clinical manifestations are associated with:

- Absence of infectious pathology or DAH in FBS, BAL or lung biopsy, and
- Absence of other possible pathogens (lung oedema, lung haemorrhage, fat embolism, leukaemic infiltration, or lung toxicity due to leucoagglutinins).

Risk factors

Myeloablative conditioning, age older than 40, and grade III–IV acute GvHD. With myeloablative HSCT, the use of TBI, especially in patients older than 40 years is an additional risk factor.

Treatment

Supportive care combined with prophylaxis and treatment of infections. Some patients improve with methylPDN and some successes have been described with anti-TNF MoAb (etanercept/infliximab).

Evolution

Up to 50–70% of patients will die due to a progressive impairment of respiratory function. This percentage reaches 97% if mechanical ventilation is required.

3.7. Multiple-organ dysfunction syndrome (MODS) (22)**Pathogenesis**

All mechanisms previously mentioned.

Incidence

Unknown, due to the difficulty in differentiating this from the syndromes already described.

Clinical features

This diagnosis should be considered when early after HSCT a patient presents two or more of the following:

- CNS dysfunction (>4 points on the scale of Folstein)
- Lung dysfunction ($O_2\text{sat} < 90\%$ in two occasions separated by more than 2 hr in the same day)
- Renal dysfunction (creatinine >1.5 mg/dL [>133 $\mu\text{mol/L}$])
- Hepatic dysfunction (VOD criteria, see 3.1.).

Treatment

There is no effective treatment and this syndrome is irreversible.

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Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. **Late-onset haemorrhagic cystitis usually is produced by:**
 - a) The direct action of cyclophosphamide on the bladder
 - b) The sum of several toxic factors that produce a bladder damage
 - c) A polyomavirus infection
 - d) A bacterial infection of the urinary tract
 - e) The neutropenia

2. **Which of the following complications could *not* be attributed to an endothelial dysfunction?**
 - a) Engraftment syndrome
 - b) Veno-occlusive disease of the liver
 - c) Haemorrhagic cystitis
 - d) Leak capillary syndrome
 - e) Thrombotic microangiopathy

3. Which of the following is *not* a clinical manifestation of VOD?

- a) Weight gain
- b) Painful hepatomegaly
- c) Ascites
- d) Platelet refractoriness
- e) Diarrhoea

4. All but one of the following are classical manifestations of engraftment syndrome, which one?

- a) Skin rash
- b) Back pain
- c) Fever
- d) Hypoxaemia
- e) Diarrhoea

5. Which is the main cause of thrombotic microangiopathy after HSCT?

- a) Bacterial infection
- b) Graft allo-reaction
- c) Immunological phenomena
- d) Cyclosporin toxicity
- e) Renal failure

NOTES