49 Hepatic Complications

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49.1 Introduction

The frequency and severity of TPH liver complications have decreased sharply in the last decade, with some complications that have completely disappeared, such as, for example, Candida liver abscesses. The development of more effective strategies to preventing SOS/VOD and GVHD has had a marked effect on its clinical presentation (see Chaps. 25 and 49). Finally, prophylaxis with antiviral and antifungal drugs has greatly reduced the incidence of the most common liver infections (Hockenbery et al. 2016). The major liver complications after HSCT are:

Early after HSCT (<100 days)	Late after HSCT (months-years)
SOS/VOD Acute GVHD (see Chap. 43) Acute hepatitis Pharmacological toxicity	Chronic GVHD (see Chap. 44) Autoimmune hepatitis Chronic viral hepatitis (see Chap. 38) Cirrhosis and hepatocellular carcinoma Iron overload (see Chap. 46) Other less frequent

49.2 Sinusoidal Obstruction Syndrome

49.2.1 Definition

SOS, formerly called 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. This syndrome is characterized by jaundice, fluid retention, and tender hepatomegaly appearing in the first 35–40 days after HSCT (Carreras 2015).

49.2.2 Pathogenesis

The hepatic metabolism of certain drugs (e.g., CY) by the cytochrome P450 enzymatic system produces several toxic metabolites (e.g., acrolein). These toxic metabolites are converted into stable (nontoxic) metabolites by the glutathione (GSH)

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enzymatic system and then eliminated. When this process occurs in patients with a reduced GSH activity, caused by previous liver disease or by the action of agents such as BU, BCNU, or TBI, which consume GSH, toxic metabolites are not metabolized. Toxic metabolites are predominantly located in area 3 of the hepatic acinus (around the centrilobular veins) because this area is rich in P450 and poor in glutathione. Consequently, damage to hepatocytes and sinusoidal endothelium occurs predominantly in this zone. Many other factors (see risk factors) can also contribute to endothelial injury.

The first events after endothelial injury caused by toxic metabolites are loss of fenestrae in sinusoidal endothelial cells (SEC), formation of gaps within and between SEC, and rounding up or swelling of SEC. Consequently, red blood cells penetrate into the space of Disse and dissect off the sinusoidal lining, which embolize downstream and block the sinusoids, reducing the hepatic venous outflow and producing post-sinusoidal hypertension. The changes observed in coagulation factors in these patients seem to be a consequence of the endothelial injury and probably play a secondary role in SOS pathogenesis, despite contributing to the sinusoidal occlusion (Carreras and Diaz-Ricart 2011).

49.2.3 Clinical Manifestations of SOS

Classical manifestations	Weight gain[a]/edema/ascites/anasarca Painful hepatomegaly/jaundice Consumption of (not refractoriness to) transfused platelets[b]
Manifestations of MOF	Pleural effusion/pulmonary infiltrates Renal, cardiac, and pulmonary failure Neurological symptoms (encephalopathy, coma)

[a]Positive fluid balance not explained by excessive hydration
[b]Difficult to demonstrate by expected thrombocytopenia

49.2.4 EBMT Diagnostic Criteria for Adults (Mohty et al. 2016)

Classical SOS (Baltimore criteria)[a]	Late-onset SOS[b]
In the first 21 days after HSCT Bilirubin ≥2 mg/dL[c] and ≥ 2 of the following – Painful hepatomegaly – Weight gain >5% – Ascites	Classical SOS beyond day 21, OR Histologically proven SOS OR ≥2 of the classical criteria AND ultrasound (US) or hemodynamical evidence of SOS

[a]These symptoms/signs should not be attributable to other causes
[b]Mainly observed after conditioning including several alkylating agents (e.g., BU, MEL, or TT)
[c]Observed in almost 100% of adults but absent in up to 30% of children

49.2.5 EBMT Diagnostic Criteria for Children (Corbacioglu et al. 2018)

No limitation for time of onset of SOS[a]
The presence of two or more of the following[b] • Unexplained consumptive and transfusion-refractory thrombocytopenia[c] • Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics or a weight gain >5% above baseline value • Hepatomegaly (best if confirmed by imaging) above baseline value[d] • Ascites (ideally confirmed by imaging) above baseline value[d] • Rising bilirubin from a baseline value on 3 consecutive days or ≥2 mg/dL within 72 h

[a]Up to 20% of children present late SOS
[b]With the exclusion of other potential differential diagnoses
[c]Weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines
[d]Suggested: imaging (US, CT, or MRI) immediately before HSCT to determine baseline value for both hepatomegaly and ascites

49.2.6 Incidence

Variable depending on the diagnostic criteria used, center experience, type of patients, and year of HSCT

Author (period analyzed) (study type)	Auto-HSCT	Allo-HSCT
Coppell et al. 2010 (1979–2007) (R)	8.7%	13%
Carreras et al. (1998) (P)	3.1%	8.9%
Corbacioglu et al. 2012 (2006–2009) (P)[a]	6%	14%
Carreras et al. 2011 (1997–2008) (R)[b]	–	MAC, 8%/ RIC, 2%

R retrospective study, *P* prospective study
[a]Only children and young adolescents
[b]Only adults

49.2.7 Risk Factors for SOS

Patient-related risk factors[a,b]	
Age	Younger < **older**
Sex	Male < female
Karnofsky index	100–90 < lower than 90
Underlying disease	Nonmalignant < malignant < **some specific diseases**[c]
Status of the disease	Remission < relapse
AST level before HSCT	Normal < increased
Bilirubin level before HSCT	Normal < increased
Prior liver radiation	No < yes
Liver status	Normal < fibrosis, cirrhosis, tumor
Iron overload	Absent < present
CMV serology	Negative < positive
Prior treatment with	**Gemtuzumab or inotuzumab ozogamicin**
Concomitant drugs	**Progestogens**, azoles
Genetic factors	GSTM1-null genotype, *MTHFR* 677CC/1298CC haplotype, etc.
Transplant-related factors	
Type of HCT	Syngeneic/autologous < **allogeneic**
Type of donor	HLA-identical sibling < unrelated
Grade of compatibility	Match < minor mismatch < major mismatch
T-cell in the graft	T-cell depleted < non-T-cell depleted
Type of conditioning	NMA < RIC < TRC < **MAC**
Busulfan	IV < oral targeted < oral CY-BU < BU-CY
TBI	Fractionated < single dose Low-dose rate < high-dose rate Less than 12 Gy < more than 12 Gy Time between CY to TBI 36 h < CY to TBI 12 h
Fludarabine	Not included < included
GvHD prophylaxis	CNI (TAC < CSA) **< CNI + sirolimus**
HSCT number	First < second HSCT

Bold characters indicate the most relevant factors
[a]Many factors have been associated with an increased risk of SOS, with those in bold letters seem the most relevant
[b]Remember that the presence of several risk factors in a patient has an additive effect
[c]Due to unknown causes, some malignant or nonmalignant diseases, osteopetrosis, adrenoleukodystrophy, thalassemia, hemophagocytic lymphohistiocytosis, or neuroblastoma are associated with a higher incidence of SOS

49.2.8 How to Confirm the Diagnosis?

SOS is a syndrome and must be diagnosed clinically, but several tools can help us	
Transjugular hemodynamic study	Permits a safe measurement of the hepatic venous pressure gradient (HVPG), which evaluates the presence of intrahepatic post-sinusoidal hypertension. A HVPG >10 mmHg is highly specific (>90%) and moderately sensitive (60%) for SOS
Transvenous liver biopsies	Transvenous biopsies may be obtained during hemodynamic studies, but false-negative results could be obtained due to the patchy nature of SOS. However, biopsies carry a risk of hemorrhagic complications (e.g., into the peritoneum and biliary tract). Consequently, they are only indicated when a crucial differential diagnosis is required (e.g., SOS versus GVHD?)

Imaging techniques	They may be helpful to confirm hepatomegaly and/or ascites (relevant in overweight patients) and for the differential diagnosis. Baseline and serial US may be useful for early detection of SOS The US abnormalities observed in SOS (hepatomegaly, splenomegaly, gallbladder wall thickening, ascites) are not specific. Decrease in velocity or reversal of the portal venous flow is considered more specific for SOS but usually occurs late in the disease (reviewed in Dignan et al. 2013)
Composite biomarkers	Recently some composite markers have shown a prognostic value at day 0 (L-Ficolin, HA, VCAM-1) and at diagnosis (ST2, ANG2, L-Ficolin, HA, VCAM-1) (Akil et al. 2015)

HA hyaluronic acid, *VCAM-1* vascular cell adhesion molecule-1, *ST2* suppressor of tumorigenicity-2, *ANG2* angiopoietin-2

49.2.9 EBMT Criteria for Severity Grading

Classically the severity of SOS was stablished, prospectively, based in a mathematical model or, retrospectively, based on its evolution (resolution or not at day +100). Later, SOS may be classified as severe with the development of multiorgan failure MOF. Several systems have been proposed for early prognostication of SOS using scales, including the following elaborated by the EBMT (Mohty et al. 2016).

	Mild	Moderate	Severe	Very severe
Time since 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 in 48 h	
Transaminases (× N)	≤2	>2 to ≤5	>5 to ≤8	>8
Weight gain (%)	<5	≥5 to <10[a]	≥5 to <10[a]	≥10
Renal function (× baseline at HSCT)	<1.2	≥1.2 to <1.5	≥1.5 to <2	≥2 or other data of MOF
This severity grading must be applied once SOS/VOD has been diagnosed applying the criteria mentioned in 49.2.4 Patients belong to the category that fulfills ≥2 criteria. 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				

N normal values

[a]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

49.2.10 Prophylaxis (Dignan et al. 2013; Carreras 2015)

Non-pharmacological measures	
Avoid modifiable risk factors: Treat Iron overload (chelation); treat viral hepatitis; delay HSCT if active hepatitis; reduce intensity of conditioning; use CY + BU instead of BU + cy; try to avoid CNI (if not possible use TAC instead CSA) for GVHD prophylaxis; avoid hepatotoxic drugs (progestogens)	
Pharmacological	*Drug (degree of recommendation)*
Not recommended	Sodium heparin (2B), low-molecular-weight heparin (2B), antithrombin III (2B), prostaglandin-1 (1B), pentoxifylline (1A)
Suggested	Ursodeoxycholic acid (2C)[a] Defibrotide: In high-risk adult patients (2B)
Recommended	Defibrotide: In high-risk children (1A) [25 mg/kg/d]

[a]In two randomized trials, UDCA reduce the incidence of SOS but in other two this effect was not observed. However, in all them, patients with UDCA have a lower TRM

49.2.11 Treatment (Degree of Recommendation) (Dignan et al. 2013; Carreras 2015)

Methylprednisolone (2C): Used by some authors. Recommended doses not defined (and range from high to low) and results difficult to analyze. Main risk: to delay treatment with defibrotide, the only agent with proved effectiveness.

Defibrotide (1B): Despite the absence of randomized studies, it is the only agent approved by FDA and EMA to treat *severe SOS* (>80% mortality). In these patients: 50% of complete remission and > 50% SRV at day +100. Early treatment strongly recommended. Dose: 6.25 mg/kg q6h in 2 h during ≥21 days, depending on the response.

49.3 Hepatitis After HSCT

Despite the reduction in the incidence of liver complications after HSCT, there remain multiple hepatic causes of elevations of serum alanine aminotransferase (ALT). In addition to the acute viral hepatitis, other noninfectious causes must be considered:

VZV, CMV, EBV, HHV-6	Infrequent (see Chap. 38)
HBV, HCV, HEV	(see Chap. 38)
Drug-induced hepatitis	Very frequent. Wide range of severity (see Sect. 49.3.1)
Hepatic GvHD	Exceptional. AST/ALT >2000 U/L usually observed in patients without or with minimal IS (or receiving DLI) (see Chaps. 43 and 44)
Autoimmune hepatitis	True autoimmune hepatitis or GVHD? Often difficult to differentiate (see Sect. 49.3.2)
Other causes	Severe SOS (see Sect. 49.2), hypoxic liver injury (septic or cardiac shock or respiratory failure), acute biliary obstruction

49.3.1 Drug Induced Hepatitis

Drug[a,b]	Comments
Thiazole antifungals[c]	Cholestatic[d] or hepatocellular hepatitis[e], liver failure
Echinocandins	Cholestatic hepatitis or mild-moderate hepatocellular hepatitis
Fluoroquinolones	Hepatocellular hepatitis
Liposomal AmB	Mild-moderate elevation of alkaline phosphatase
TMP/SMX	Hepatocellular hepatitis
CSA, tacrolimus	Cholestasis. Dose-dependent effect
Rapamycin	Hepatocellular damage, increased risk of SOS[f]
Anticonvulsants	Hepatitis, hepatocellular or cholestatic
NSAIDs	Hepatitis, hepatocellular or cholestatic
Acetaminophen	Hepatocellular hepatitis. Dose-dependent effect
Antidepressants	Hepatocellular hepatitis. Unrelated to drug dosage
Ranitidine	Cholestatic hepatitis, eosinophilic infiltration
Amoxicillin-clavulanic acid	Cholestatic and/or hepatocellular hepatitis
Antihypertensive drugs + lipid-lowering agents + oral hypoglycemics	Drugs usually associated in patients with metabolic syndrome (see Chap. 55)

AMB amphotericin B, *TMP/SMX* trimethoprim-sulfamethoxazole, *NSAID* nonsteroidal anti-inflammatory drug

[a]Other than cytostatic drugs

[b]Online resources for the consultation of toxicities and interactions: https://livertox.nlm.nih.gov

[c]Voriconazole, posaconazole

[d]Liver damage with predominant elevation of bilirubin and alkaline phosphatase

[e]Hepatic damage with predominant elevation of transaminases

[f]Especially if associated to CNI

49.3.2 Autoimmune Hepatitis (AIH)

The main problem with this hepatitis is how to differentiate them from a hepatic GVHD, since pathogenesis, clinical manifestations, and biological changes are practically identical (Dalekos et al. 2002).

	Autoimmune hepatitis	Hepatic GVHD
Jaundice	Usually mild	Various degrees
Other symptoms	Fatigue, malaise, many times asymptomatic	Hepatic tenderness, dark urine, acholic stools, anorexia, usually **GVHD in other organs**
Pathology	Inflammatory infiltrate in portal area, often penetrating lobes	Inflammatory infiltrate, **loss of small bile duct, degeneration of bile ductular epithelium**, cholestasis
Cirrhosis	May be present	Rare
>AST	Moderate to severe	Less striking

	Autoimmune hepatitis	Hepatic GVHD
>GGT	Marked	Usually normal o decreased
Auto-Ab	Type AIH-2 (**ALKM, ALC-1**)	Often found (AIH-1) (ANA, ANCA, etc.)
Response to steroids	Excellent	Depends on severity

In bold letter main differential data

49.4 Cirrhosis and Heparocellular Carcinoma

Cirrhosis[a]	– In HSCT with HBV: exceptional – In HSCT with HCV: 11% at 15 years; 20% at 20 years (Peffault de Latour et al. 2004)[b] – In HSCT with HEV: frequency not known but rapidly progressive cases have been reported (see Chap. 38) – Poorly compensated cirrhosis is a contraindication for HSCT because of the prohibitive risk of developing SOS after MAC. Even compensated cirrhosis has a high likelihood of hepatic decompensation after NMA (Hogan et al. 2004)
Carcinoma	In patients with chronic HCV: 5% at 20 years of new cases per year (Peffault de Latour et al. 2004). These patients should undergo surveillance with six monthly liver ultrasound scans according to international guidelines

[a]These data correspond to the times when new antiviral agents were not available. No updated data are available
[b]The cumulative incidence of severe liver complications in HSCT infected with the HCV was 11.7% at 20 years in multicenter cohort (Ljungman et al. 2012)

49.5 Other Less Frequent Hepatic Complications

49.5.1 Nodular Regenerative Hyperplasia

After HSCT, occasionally observed in patients with a previous SOS/VOD.

Pathogenesis: Probable consequence of changes in liver blood flow with atrophy of zone 3 of the acinus and hypertrophy of zone 1 (without fibrosis).

Clinical Manifestations: Silent evolution (occasionally increase of AP) until the appearance of portal hypertension (ascites, splenomegaly, thrombocytopenia).

Diagnosis: Investigated by imaging (primarily MRI). Liver biopsy can rule out carcinoma and cirrhosis; need for a needle biopsy (not transjugular or fine-needle biopsy).

49.5.2 Focal Nodular Hyperplasia

In one series (Sudour et al. 2009) of HSCT survivors undergoing liver MRI, these lesions were observed in 12%.

Pathogenesis: The likely cause is sinusoidal injury caused by myeloablative conditioning regimens.

Clinical Manifestations: Asymptomatic.

Diagnosis: By MRI, lesions have characteristic central scars that differentiate them from hepatocellular carcinoma and fungal lesions.

49.5.3 Idiopathic Hyperammonemia

Very rare. Observed after conditioning (Frere et al. 2000)

Diagnosis: Severe hyperammonemia (>200 µmol/L) with minimal alteration of other LFTs.

Clinical Manifestations: Lethargy, motor dyscoordination, and alkalosis.

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