Acute and Late complications after Allogeneic Stem Cell Transplantation

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STEM CELL TRANSPLANTATION

BHS

Plan of the exposal

Acute complications

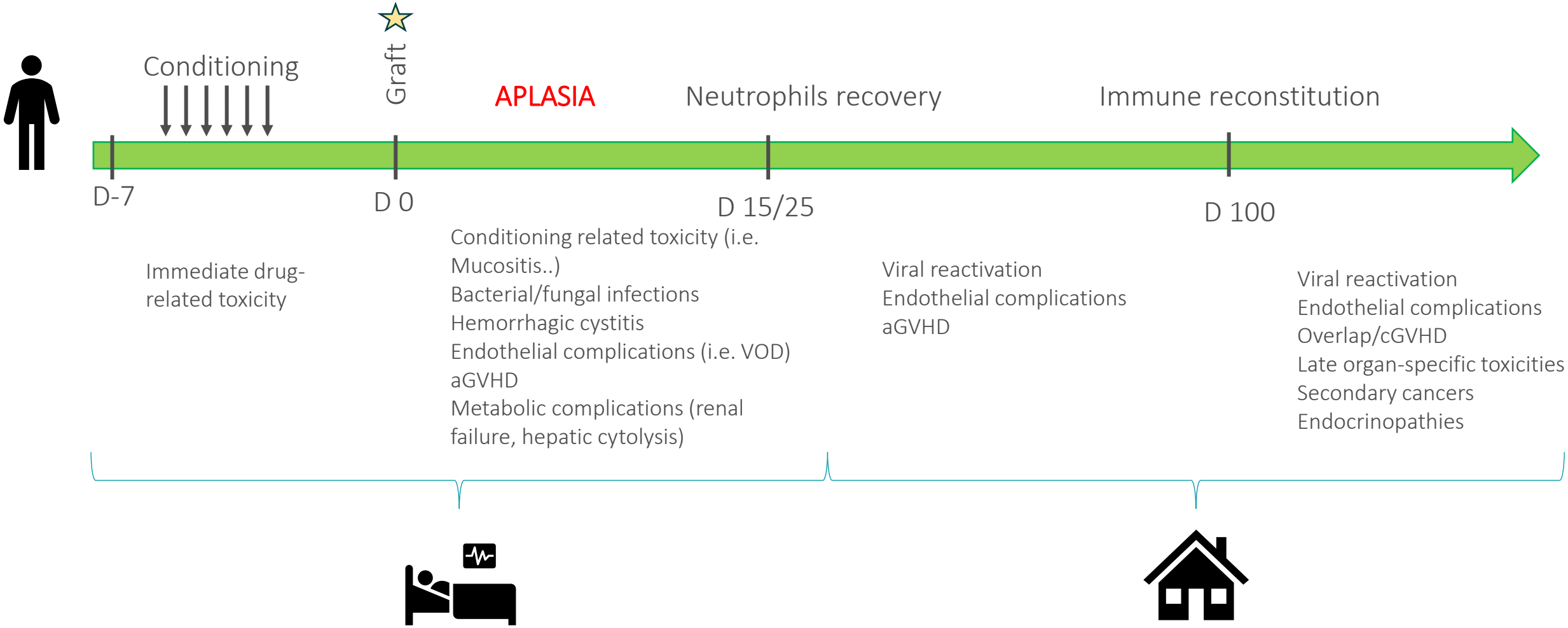
- Infectious
- Endothelial complications
- Chemo/radio toxicities

Late complications

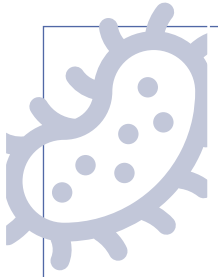
- Secondary cancers
- Organ specific late complications

Take home messages

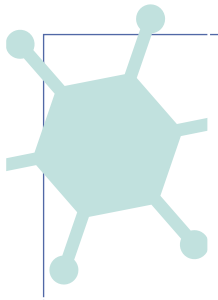
HSCT Patient journey



Acute complications

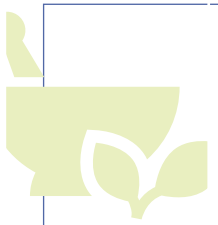


Bacterial and fungal Infectious complications

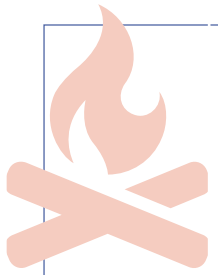


Viral reactivation and complications
- CMV reactivation
- EBV reactivation (PTLD)
- Viral Hemorrhagic cystitis

Endothelial complications
- VOD/SOS
- Thrombotic microangiopathy
- Capillary leak syndrome
- Alveolar hemorrhage
- Posterior Reversible Encephalopathy syndrome

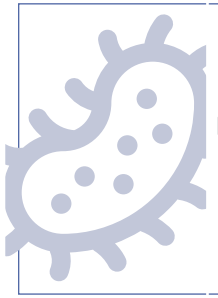


Chemo-radiotherapy related direct toxicities
- Mucositis
- Hemorrhagic cystitis
- Other (renal failure, hepatic cytolysis...)

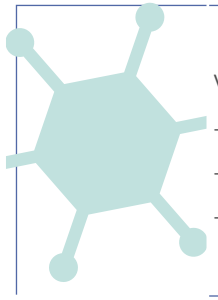


aGVHD/cGVHD

INFECTIONS



Bacterial and fungal Infectious complications



Viral reactivation and complications
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- EBV reactivation (PTLD)
- Hemorrhagic cystitis

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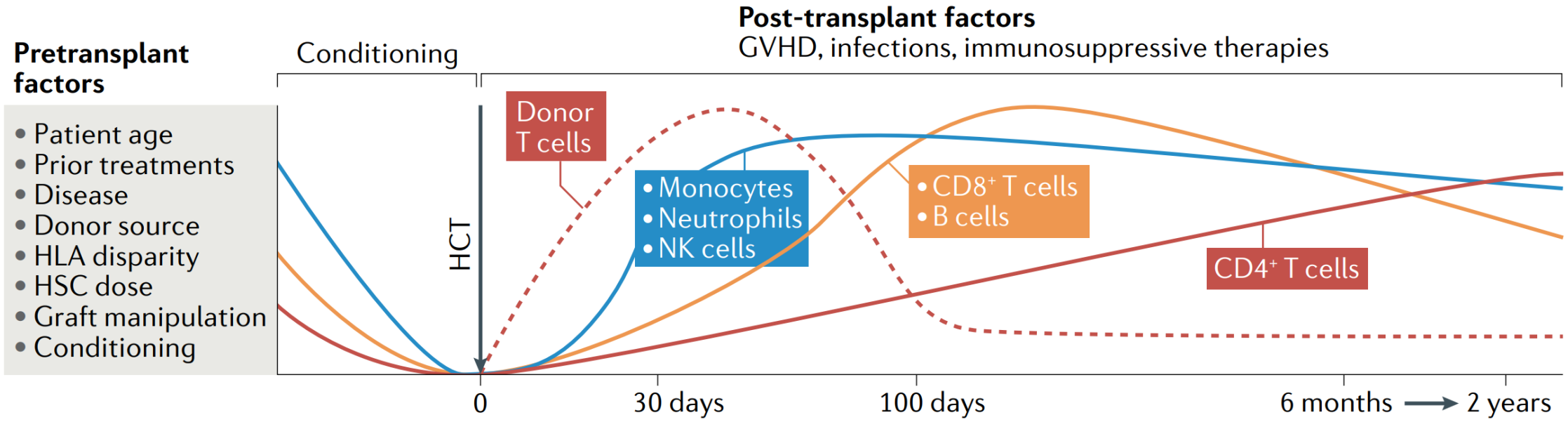
Immune reconstitution post allogeneic stem cell transplantation



Normal number of cells doesn't mean normal functional cells

Velardi et al Nat Rev Imm 2021

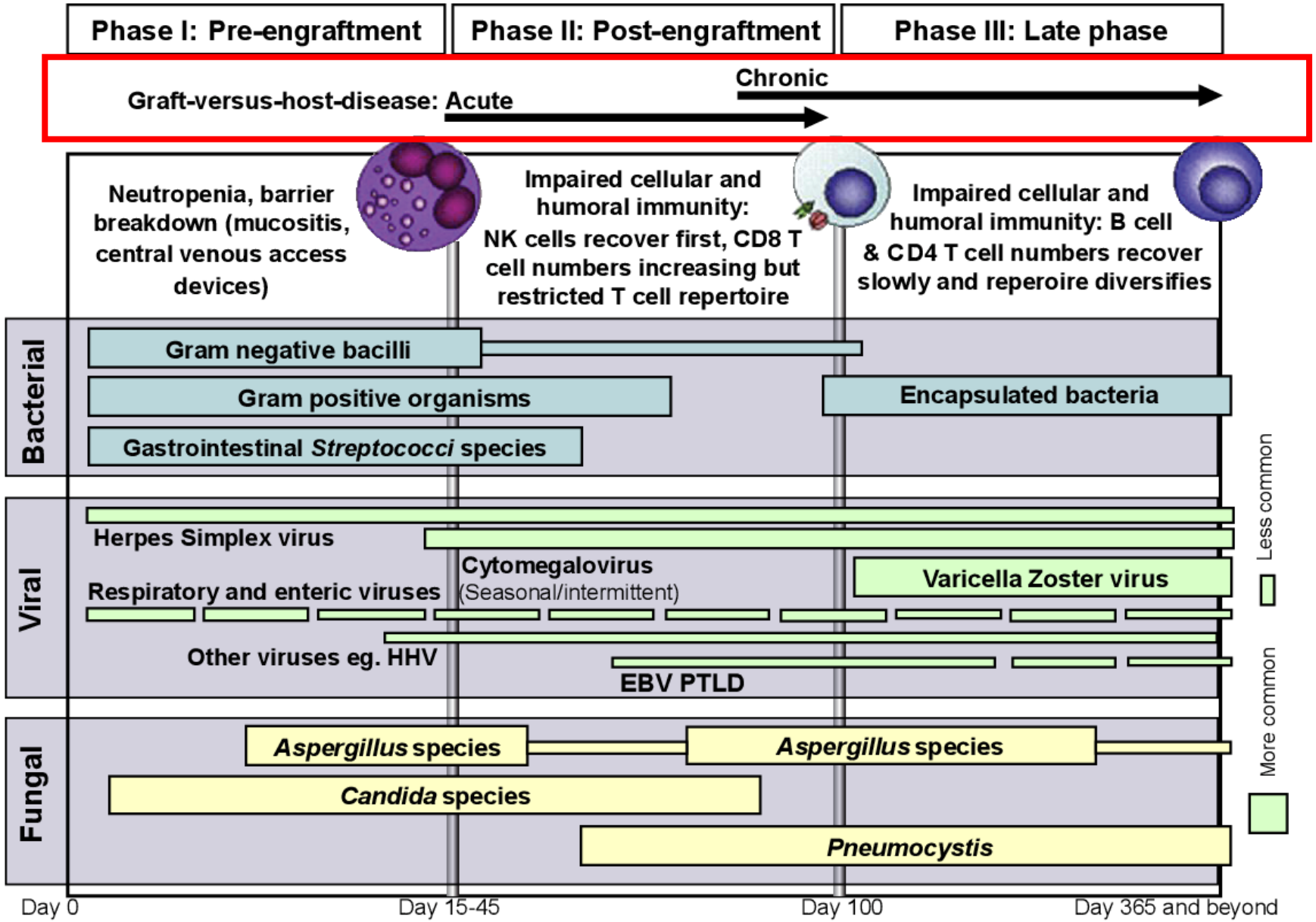


Figure 1: Phases of opportunistic infections among allogeneic HSCT recipients.

Khedia et al Journal of Stem Cell Research & Therapy 2013

Prophylaxis in HSCT recipient

Pathogen	Prophylaxis	Duration
HSV/VZV	Aciclovir 400 mg tid	12 mo after HSCT
CMV in CMV+ recipients	Letermovir 480 mg/d (or 240mg/d if concomintant ciclosporine)	Until D+100
Fungi	High risk (AML/MDS, GVHD under steroids) : posaconazole tablets 300 mg/d Others: Fluconazole/itraconazole	Until engraftment or if until steroids discontinuation
Pneumocystis	Pentacarinat aerosol at D-1. Trimethoprim-sulfamethoxazol 800/160 3x week from engraftment	6-12 mo after HSCT
Toxoplasmosis	Trimethoprim-sulfamethoxazol 800/160 3x week from engraftment	6-12 mo after HSCT

A.M. 37yo female, D+8 post HSCT

Aplasia phase: *Hb : 6.8 gr/dl, WBC: 0/mcl, Plt: 24000/mcl*

R/B-ALL, Phi neg, in CR2 after Inotuzumab. Geno-HSCT, female/female, A+/O+, CMV+/+, PBSC.

Conditioning: TBI 12Gy – Endoxan 120 mg/kg (MAC)

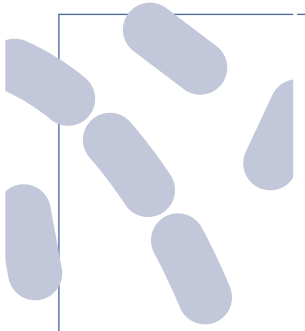
GVHD prophylaxis: Ciclosporine and MTX

G4 Mucositis

Fever 38.7°C → Neutropenic Fever

Start empiric antibiotic therapy: Piperacillin-tazobactam

Neutropenic fever in HSCT patients, approach



Antibiotic resistant bacteria risk

- Known colonisation (i.e. Anorectal swabs)
- Previous antibiotherapy
- Local epidemiology

Clinical situation

- shock, hemodynamic instability
- clinical evidence of infection (KT, skin infection, mucositis...)

Neutropenic fever – Long neutropenia > 10 days

- IV Antibiotic active on Pseudomonas species

- Start with larger coverage antibiotic if EBSL carrier (Meropenem) → de-escaladate to pip-tazo or cefepim after 72-96h if no ESBL pathogen and resolution of fever

- Don't escaladate (i.e. Pip-tazo → meropenem) in absence of microbiological documentation or clinical degradation, even if fever persists

- Early and aggressive work-up

If fever persist after 72-96h of antibiotic therapy, without documentation:

i. Check for alternative causes of fever (fungal infection, viral infection...)

ii. Discuss antifungal empiric treatment

iii. Condition explaining persistant fever (mucositis, colitis...)

M.S. 46 yo - Follow-up visit 3,5mo after HSCT

Haploidentical HSCT, female donor (daughter), PBSC as graft source, ABO: A+/A+, CMV-/CMV+.

AML with MDS-related changes

Conditioning: TBF + PTCY

Problem: worsening pancytopenia, asymptomatic patient.

<u>3mo after HSCT</u>

Hb : 10.5 gr/dl

WBC: 3500/mcl, NAC : 2700/mcl

Plt: 65000/mcl

<u>3,5 mo after HSCT</u>

Hb : 9.5 gr/dl

WBC: 1600/mcl, NAC : 670/mcl

Plt: 35000/mcl

Pancytopenia after HSCT

Graft rejection

Full donor chimerism at 3mo post HSCT

Viral infection

CMV
EBV
AdenoV
B19

CMV viral load > 60.000 copies/ml

Drug toxicites

No new drugs

Vitamine deficiency

B12, folates, zinc normal

Disease relapse

Bone marrow performed at 3mo post HSCT without blasts

Cytomegalovirus

Double strand DNA virus

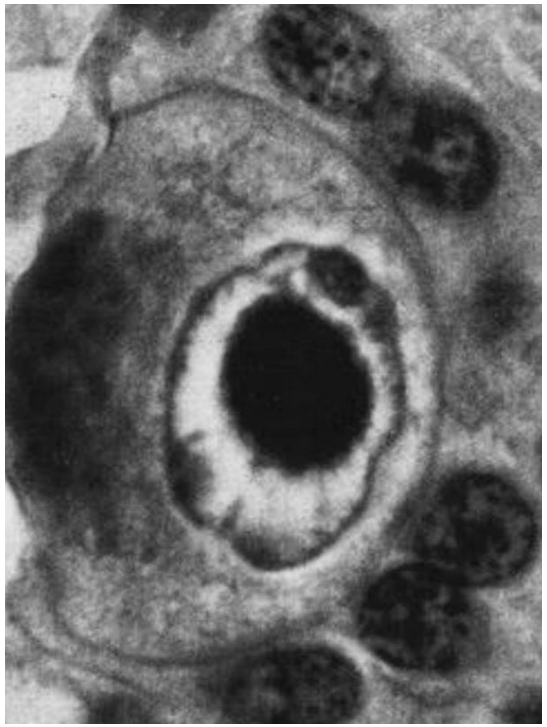
β-herpesvirus (HHV-5)

Primary infection asymptomatic in immunocompentent

Seroprevalence 50-100%

Persists in a latent state for life in monocytes, lymphocytes, CD34+ cells (and other cells??)

Reactivation occurs generally in first 100 days after HSCT (but later reactivations are also possible)



Crough et al, Clin Microbiol Rev. 2009
Krech et al, Bull World Health Organ 1973
Ho, Med Microbiol Immunol 2008

Definitions

CMV Infection

Virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen.

Primary CMV infection – in a previously CMV negative patient

Recurrent CMV infection – if prior CMV+ patient

CMV Disease

Clinical symptoms and/or signs of organ disease combined with CMV virus isolation in involved organ.

(Most common GI disease)

Ljungman Clin Inf Dis 2017

Risk factors for CMV infection in HSCT recipients:

Serological status (D-/R+ > D+/R+> R-)

T-cell depletion (ATG), PTCy

HLA Mismatch – MMUD, Haplo

GVHD – Prednisone > 1mg/kg/day

A CMV+ donor should be chosen when possible for a CMV+ recipient

Ljungman Clin Infect Dis. 2014

Pre-emptive therapy: How to detect CMV infection?

Monitoring CMV PCR in blood test 1x week and treat if reactivation occurs.

(From D0 through D100)

Significant different values- PCR: 3x difference

Ex. 300 UI/ml and 500 UI/ml = no difference

300 UI/mL and 1000 UI/ml → Increasing CMV viral load

Prophylaxis with Letermovir

Letermovir reduced clinically significant cytomegalovirus infections and all-cause mortality at week 24 versus placebo in CMV+ recipients.

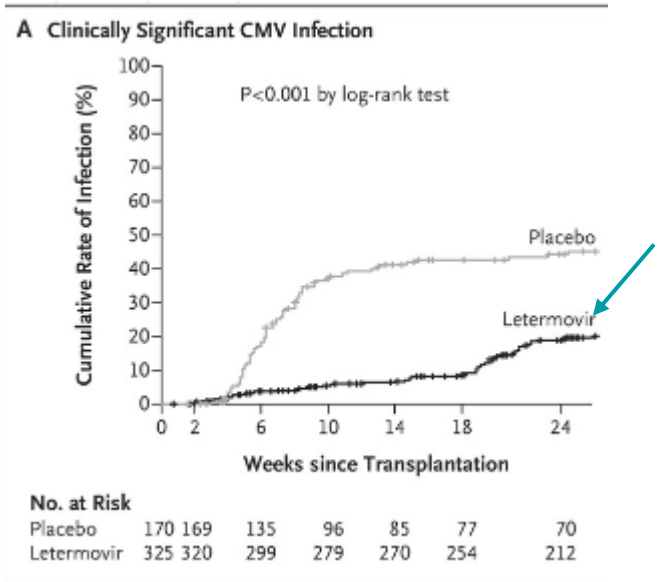
Letermovir in practice:

For all CMV+ recipients

D0 through D+100 post HSCT

480 mg/d (240 mg /d if ciclosporine)

Monitor patients after Letermovir withdrawal – reactivation are possible



Marty et al NEJM 2017

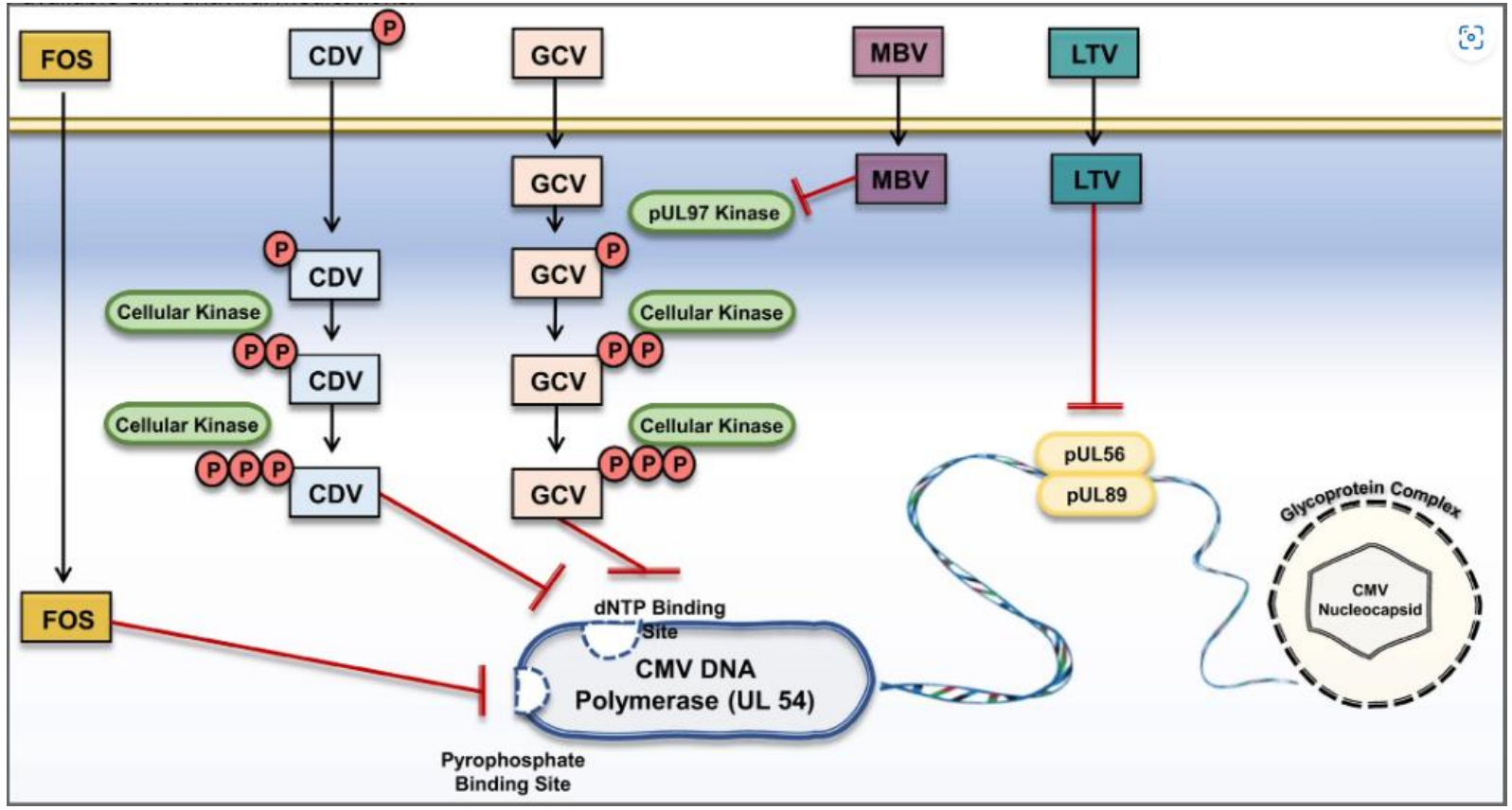
Antiviral treatments in CMV infection

GCV = Ganciclovir

FOS= foscavir

MBV = maribavir

LTV = letermovir



Dickter et al JCTF 2022

Treatment

Ganciclovir – 1st LINE	
Mechanism	CMV DNA Poly Inhibition
Indication	1st line CMV disease/infections HHV6 Aciclovir R HSV
Administration	IV 5 mg/kg/day (VALcyte PO 900 mg 2x day – no Oral form if GVHD+)
Duration	At least 2 weeks Until negative viral load
Metabolism	Renal elimination
Adaptation	Renal function
Toxicity	Hematological -GCSF to treat neutropenia - Transfusions

Foscavir - NOT remboursed	
Mechanism	CMV DNA Poly Inhibition
Indication	CMV disease/infections HHV6 Aciclovir R HSV
Administration	Poor disponibility PO IV: 90 mg/kg/dose every 12h
Duration	At least 2 weeks Until negative viral load
Metabolism	Renal elimination
Adaptation	Renal function
Toxicity	Renal – tubular Electrolytes disturbaces Seizures Genital ulcers

Maribavir – 2nd line remboursed from 1/3/2024	
Mechanism	CMV pUL97 kinase inhibition
Indication	CMV
Administration	PO 400 mg twice/day
Metabolism	Hepatic metabolism
Duration	8 weeks
Adaptation	-
Toxicity	Nausea, GI disturbances

Refractory CMV and Resistant CMV

Table 2. Summary of the Definitions of Refractory Cytomegalovirus Infection and Disease and Antiviral Drug Resistance for Use in Clinical Trials

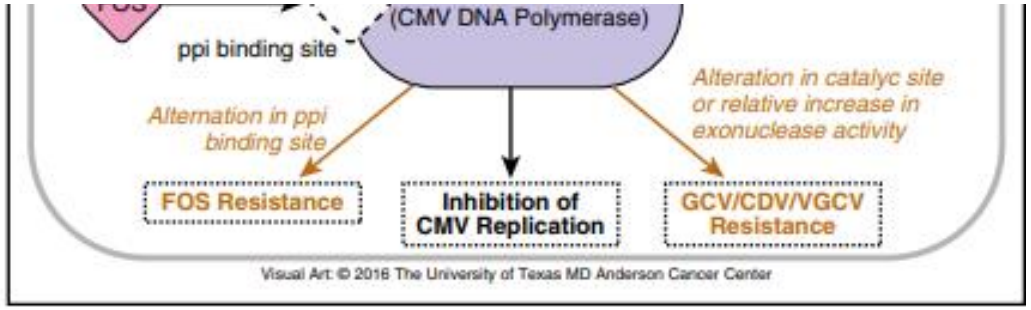
Term	Definition
Refractory CMV infection	CMV viremia that increases[a] after at least 2 wk of appropriately dosed antiviral therapy
Probable refractory CMV infection	Persistent viral load[b] after at least 2 wk of appropriately dosed antiviral therapy
Refractory CMV end-organ disease	Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy
Probable refractory CMV end-organ disease	Lack of improvement in signs and symptoms after at least 2 wk of appropriately dosed antiviral drugs
Antiviral drug resistance	Viral genetic alteration that decreases susceptibility to one or more antiviral drugs[c]

Abbreviation: CMV, cytomegalovirus.

[a]More than 1 $\log_{10}$ increase in CMV DNA levels in blood or serum and determined by $\log_{10}$ change from the peak viral load within the first week to the peak viral load at ≥2 weeks as measured in the same laboratory with the same assay.

[b]CMV viral load at the same level or higher than the peak viral load within 1 week but <1 $\log_{10}$ increase in CMV DNA titers done in the same laboratory and with the same assay.

[c]Known examples involve genes involved in antiviral drug anabolism (eg, UL97-mediated phosphorylation of ganciclovir), the antiviral drug target (eg, UL54, UL97, UL56/89/51), or compensation for antiviral inhibition of biological function (eg, UL27).



El Chaer et al Blood 2016

CMV infection

At Risk : CMV+ recipients

Prophylaxis with Letermovir (3mo post HSCT) in CMV+ recipients

Pre emptive strategy

GCV → hemato tox

FOS → renal tox

MAR → 2° L remboursed in Belgium

In 2w viral load should decrease

Look for mutations in case of refractory disease

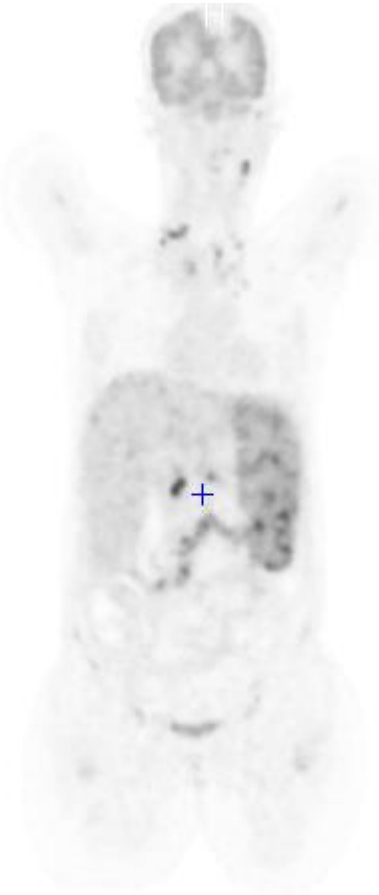
S.V. 35 yo

2 months post HSCT

Severe aplastic anemia, genoidentical HSCT, male/female, A+/A+, CMV+/CMV+, EBV-/EBV+.

Fever and adenopathies

- Hb 10.5 gr/dL, Plt 120000/mcl, WBC 3500/mcl
- EBV viral load 140000 copies/mL
- PET CT: Lymphoma stage IV
- Anapath: Aggressive EBV+ B Lymphoma



Post transplant Lymphoproliferative Disease (PTLD)

Post HSCT or solid organ transplant

Heterogeneous group of lymphoproliferative disorders

70% EBV positive, donor-derived

1st year post HSCT in 80% of cases → After 1y = Late Onset PTLD

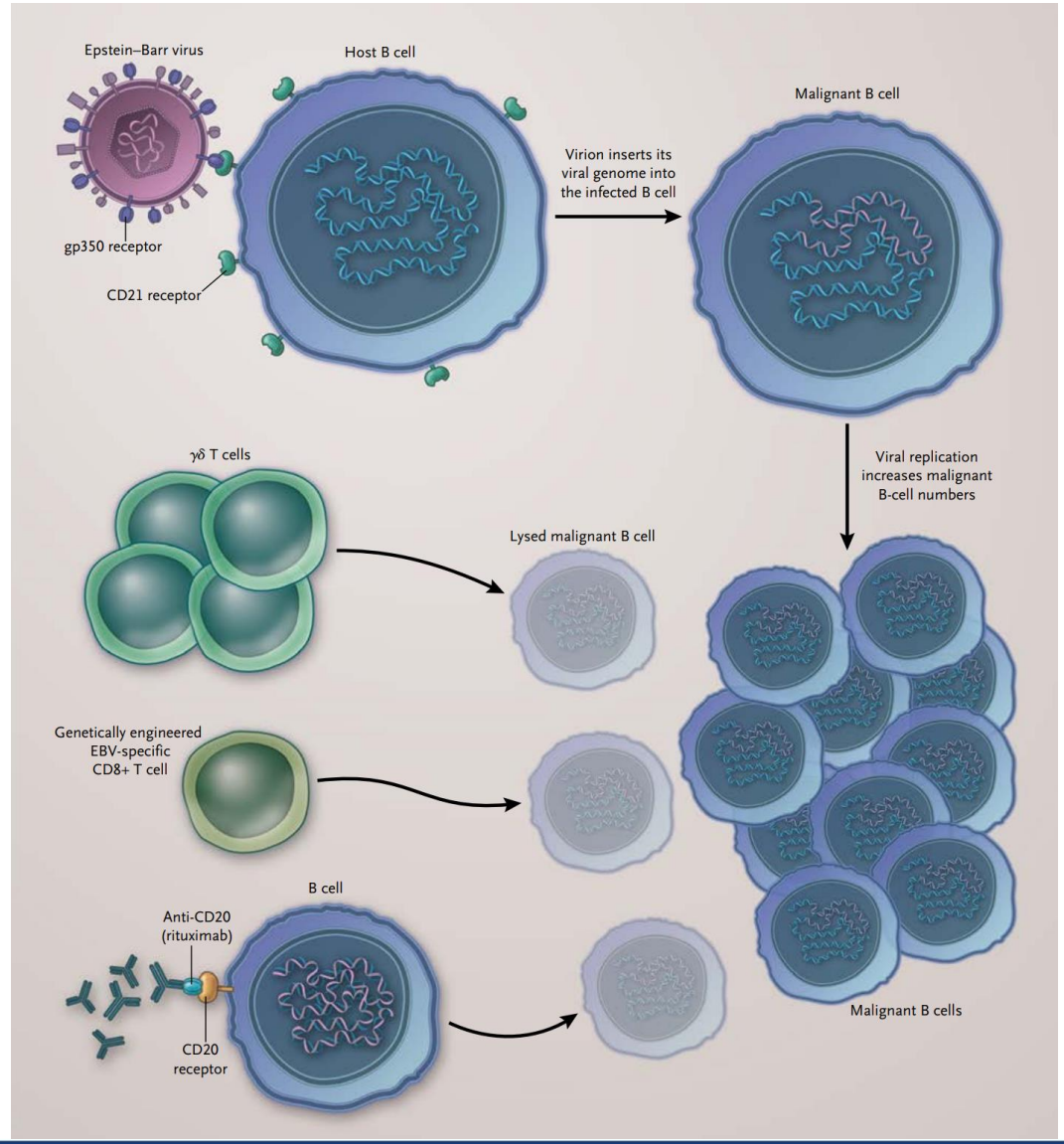
Risk Factors
EBV positive donor, EBV negative recipient
Bone marrow and cord blood as stem cell source
Unrelated donor, mismatched donor
T-cell depletion in vivo/vitro (i.e. ATG, alemtuzumab)
Chronic GVHD (Late onset PTLD)

Curtis et al Blood. 1999

Leblond J Clin Oncol. 1998

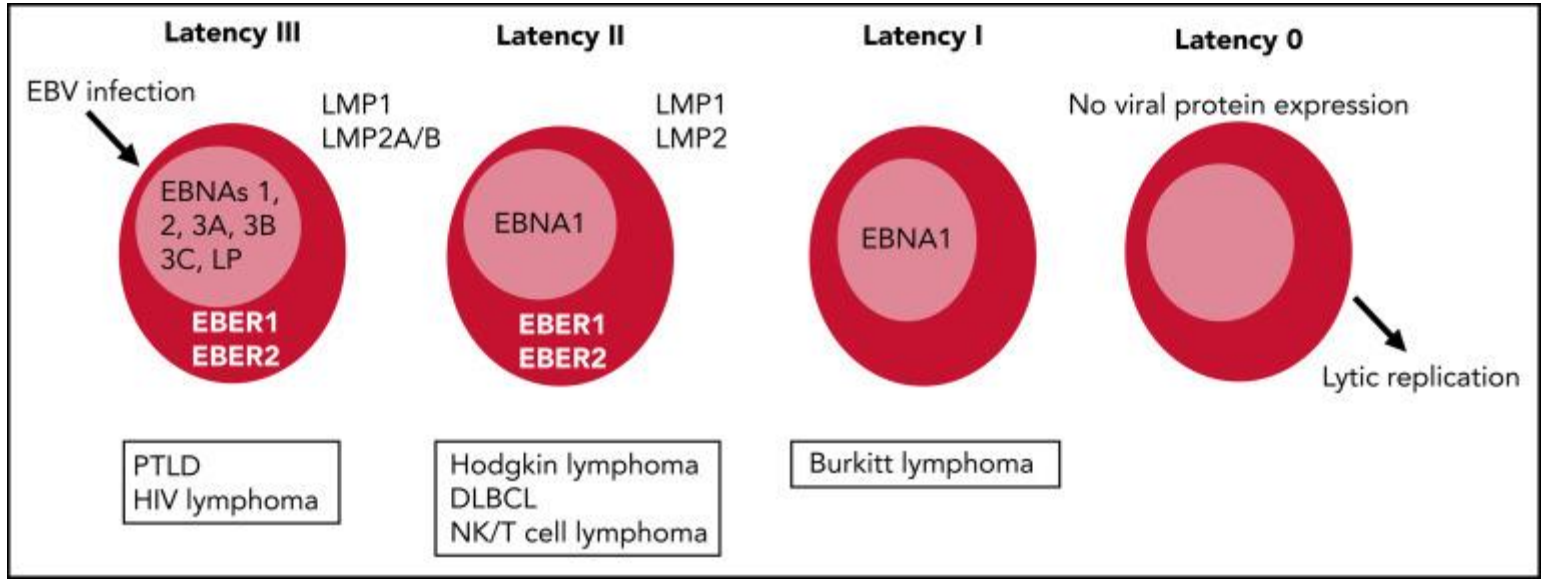
Epstein Barr Virus (EBV)

- double-stranded DNA virus
- γ-herpesviridae subfamily
- Cancerigen virus, 1–2% of all tumours in humans and ~200,000 new cancers per year
- Not Only B-Lymphomas but also other tumors (nasopharingeal cancer)
- 90% EBV+ - latency in B-cells



Cohen et al Sci. Transl. Med 2011
Cesarman Ann Rev Path 2014
Dharnidharka et al NEJM 2015

EBV Latency in B-cells



Immunosuppression

=

impaired cell-mediated immunity

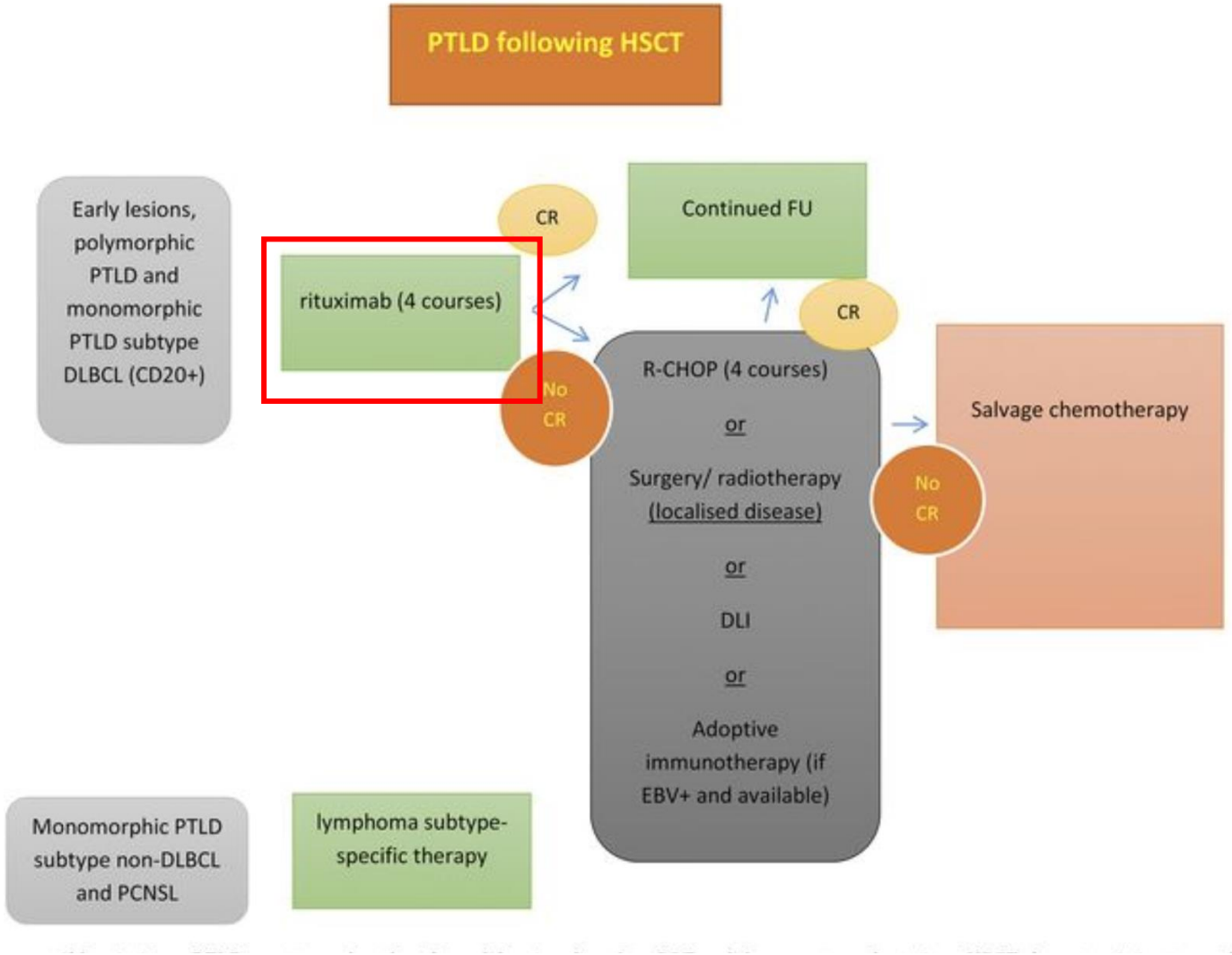
Table 2. Classification of Post-Transplantation Lymphoproliferative Disorder (PTLD) by the World Health Organization (WHO).*

Characteristic	Nondestructive PTLD†	Polymorphic PTLD	Monomorphic PTLD	Hodgkin's Lymphoma–like PTLD
Underlying architecture	Nondestructive	Destructive	Destructive	Destructive
Composition	Plasma cells, small lymphocytes, immunoblasts	Complete spectrum of B-cell maturation	Fulfills specific WHO criteria for NHL; mantle-cell and follicular NHL are not considered PTLD	Fulfills specific criteria for classic Hodgkin's lymphoma
Immunohistochemical features	No diagnostic value	Mixture of B cells and T cells	Monoclonal population 90% DLBCL, mostly CD20+ (majority ABC type)	CD20–, CD30+; most cases CD15+
EBV association	Almost 100%	>90%	Both EBV-positive and EBV-negative	>90%
Clonality	No in most cases	Variable	Yes	Yes
Molecular genetic findings	None	Variable (BCL6 somatic hypermutations)	Differences between EBV-positive (genomic stable) and EBV-negative (similar to DLBCL in immunocompetent patients)	No information available
Clinical features	Mostly early PTLD	Variable	Both early and late PTLD	Possible increase in incidence of late-onset Hodgkin's lymphoma after allogeneic HSCT

* Information is from Swerdlow et al.[26,27] ABC denotes activated B-cell, DLBCL diffuse large B-cell lymphoma, NHL non-Hodgkin's lymphoma, and WHO World Health Organization.
† Nondestructive PTLD includes plasmacytic hyperplasia PTLD, infectious mononucleosis–like PTLD, and florid follicular hyperplasia PTLD.

Dierickx et al NEJM 2018

Treatment



Dierickx et al NEJM 2018

Pre emptive therapy

Table 7. Recommendations for preemptive therapy of EBV disease.

Recommendations for preemptive therapy of EBV disease
• Significant EBV DNA-emia without clinical symptoms of EBV disease is an indication for preemptive therapy with rituximab (BIIu).
• No specific threshold of EBV DNA-emia can currently be recommended for initiation of preemptive therapy.
• Rituximab once weekly (1-4 doses) is recommended until EBV DNA-emia negativity (AIIu).
• Rituximab should be combined with reduction of immunosuppression, if possible (AIIu).
• Donor or third party EBV-specific cytotoxic T lymphocytes (CTL) should be considered, if available (CIIu).
• Antiviral drugs are not recommended for preemptive therapy (DIIh).

Pre emptive treatment reduce the risk of PTLD-related death

Which threshold? 1000 copies/ml vs 10000 copies/ml, versus 40000 copies/ml

Styczynski et al Haematologica 2016
Styczynski et al Trans Inf Dis 2009

Practice

- Blood PCR EBV quantification 1x/week during first 3mo, than at each visit (1-2x/months) during the first year
- Continue in specific population (GVHD patients, cord blood/Bone marrow as source of CS)
- If PCR EBV < 10000 copies/ml F-U
- if PCR EBV> 40000 copies/ml or >10000/ml in short time → start Rituximab
- Treat with rituximab 375 mg/m2/week, maximum 4 doses
- PET CT in case of clinical evidence of lymphoma, high PCR EBV levels (i.e. >100000 copies/ml) or persistance of EBV viral load despite 4x Rtx.

C.D. male 45 yo

10 days after HSCT

Haploidentical HSCT, PBSC as graft source

DN-AML

Conditioning: TBF + PTCY

Hb : 7.3 gr/dl, WBC: 0/mcl, Plt: 12000/mcl

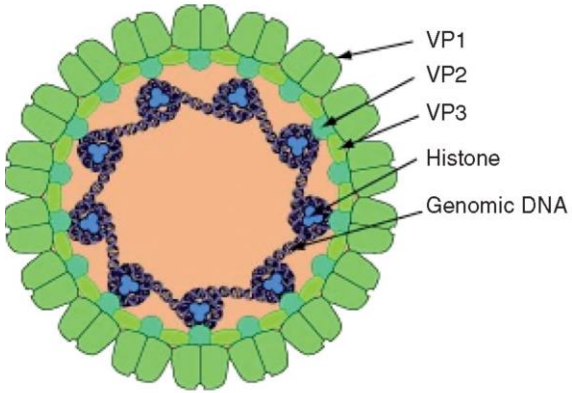
Dysuria and hematuria, no other symptoms

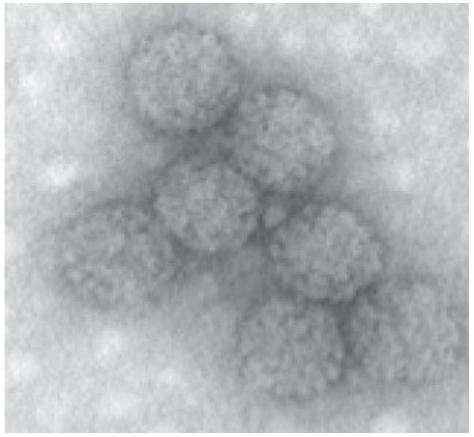
Examen: Urines mi-jet	
Tigette mi-jet	
Glucose:	Absence
Acétone:	Traces
Protéines:	+
Sang:	+++
pH urinaire:	5.5
Bilirubine:	Absence
Nitrites:	Absence
Urobilinogène:	++
Densité:	1.030
Leucocytes estérase:	Absence
Sédiment urinaire mi-jet	
Leucocytes:+ 18 /µL (Norme:<10)	
Erythrocytes:+ 889 /µL (Norme:<12)	
Cell. épithéliales:	Absence
Cell. voies urinaires supér.:	Absence
Cristaux:	Absence
Cylindres hyalins:	Absence
Cylindres pathogènes:	Absence
Bactéries:	+
Levures:	Absence
Culture aérobie mi-jet	
	Négatif

BK polyomavirus Viruria

Hemorrhagic Cystitis

5 to 25 % of patients after HSCT





Late >1 week after HSCT

BK polyomavirus (BKPyV-HC)

80% of all HSCT patients develop high-level BKPyV viruria, while only 5%–20% develop BKPyV-HC

Other pathogens: adenovirus, herpes virus, CMV, bacteria…

Criterion	Definition
1	clinical symptoms/signs of cystitis, such as dysuria and lower abdominal pain
2	haematuria grade 2 or higher
3	BKPyV viruria of >7 $\log_{10}$ copies/mL[a]

[a]Plasma viral loads of >3–4 $\log_{10}$ copies/mL are found in more than two-thirds of episodes of BKPyV haemorrhagic cystitis.

Sharma 2014

BKPyV- Hemorrhagic cystitis

Best supportive therapy

Hydratation

Increase platelet threshold

Antispasmodic drugs

Consider reduction in IS

Check renal function, hemogram, viraemia

Kidney US to rule out intravesical blood clots and hydronephrosis

Severity	Symptoms
Grade 1	Microscopic hematuria
Grade 2	Macroscopic hematuria
Grade 3	Macroscopic hematuria with small clots
Grade 4	Gross hematuria with clots causing urinary obstruction requiring instrumentation for clot evacuation and/or causing urinary obstruction

Grade I-II

Consider bladder irrigation

Grade III-IV or viremia

Bladder irrigation

Intravenous cidofovir

Cystoscopy

Consider hyperbaric Oxygen therapy

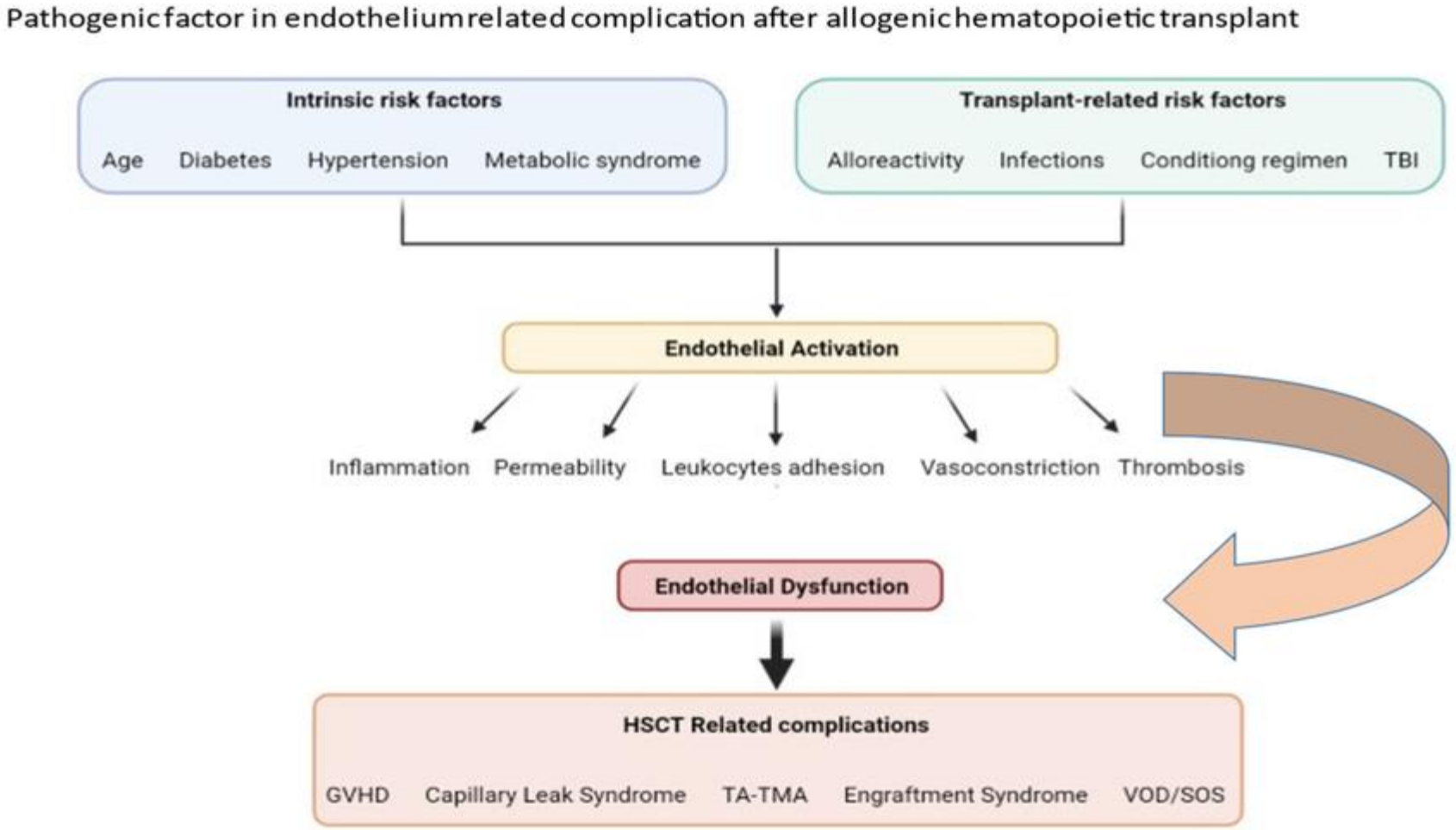
Consider embolisation

ENDOTHELIAL COMPLICATIONS

Endothelial complications

- VOD/SOS
- TMA
- Capillary leak syndrome
- Alveolar hemorrhage
- Posterior Reversible Encephalopathy syndrome
- Engraftment syndrome

Endothelial complications



Milone et al Journ Clin Med 2022

C.R. 44yo female, D+10 post HSCT

Aplasia phase: Hb 9.2 gr/dl, WBC 0/mcl, Plt 13000/mcl

AML with BCOR mutation, in CR1 (Gemtuzumab ozogamicine given in induction)

MRD allo-HSCT, female/female, B+/A+, CMV-/CMV+.

Conditioning: Fludarabine/Busulfan4 (MAC)

GVHD prophylaxis: Ciclosporine/MMF

D+7: Mucositis G3

D+8 : Febrile Neutropenia --> Piperacilline Tazobactam

D+10 : Weight gain (65 kg, +4kg in 3 days), ascites, painful hepatomegaly, SpO2 90% → 2lt/min O2, Bili 4.6 mg/dl, Creat 1.25mg/dl

Hepatic sinusoidal obstruction syndrome (SOS)

Veno-occlusive disease (VOD)

- Systemic endothelial disease
- Rapid weight gain, ascites, painful hepatomegaly, and jaundice.
- Platelet refractoriness and renal failure common.
- From mild to life-treathening severity
- 65% mortality, death related to multi-organ failure rather than liver failure.

Bearman et al Blood 1995
Coppell et al Biol Blood Marrow Transplant. 2010

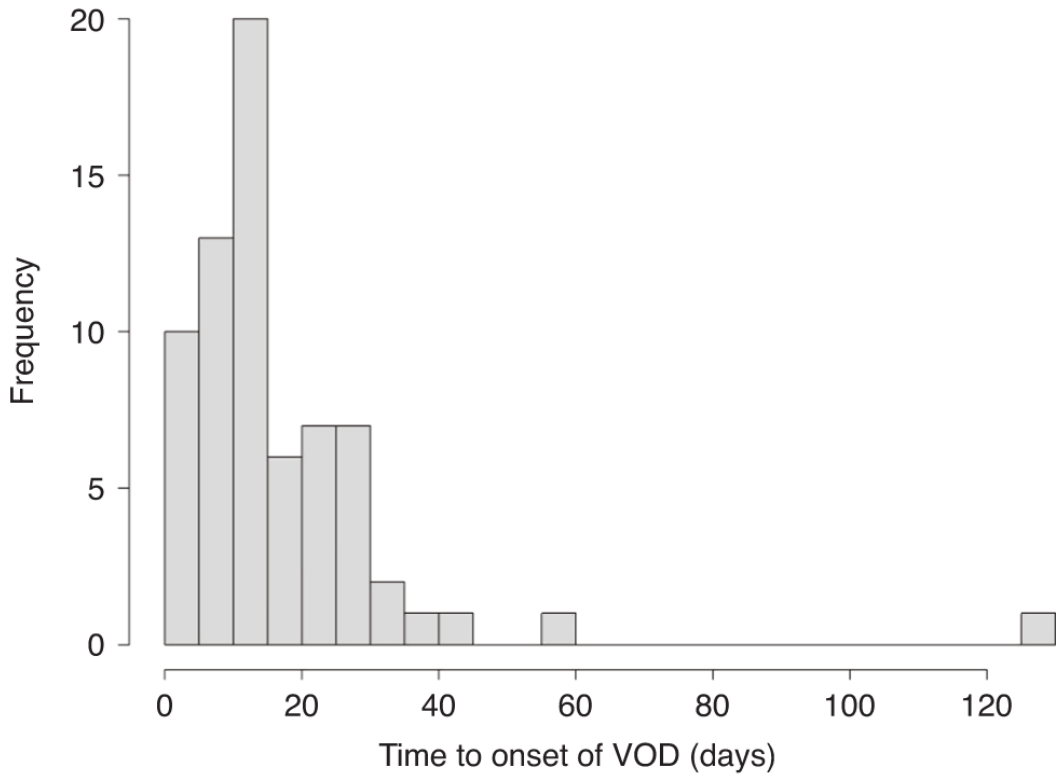
Risk Factors for VOD

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

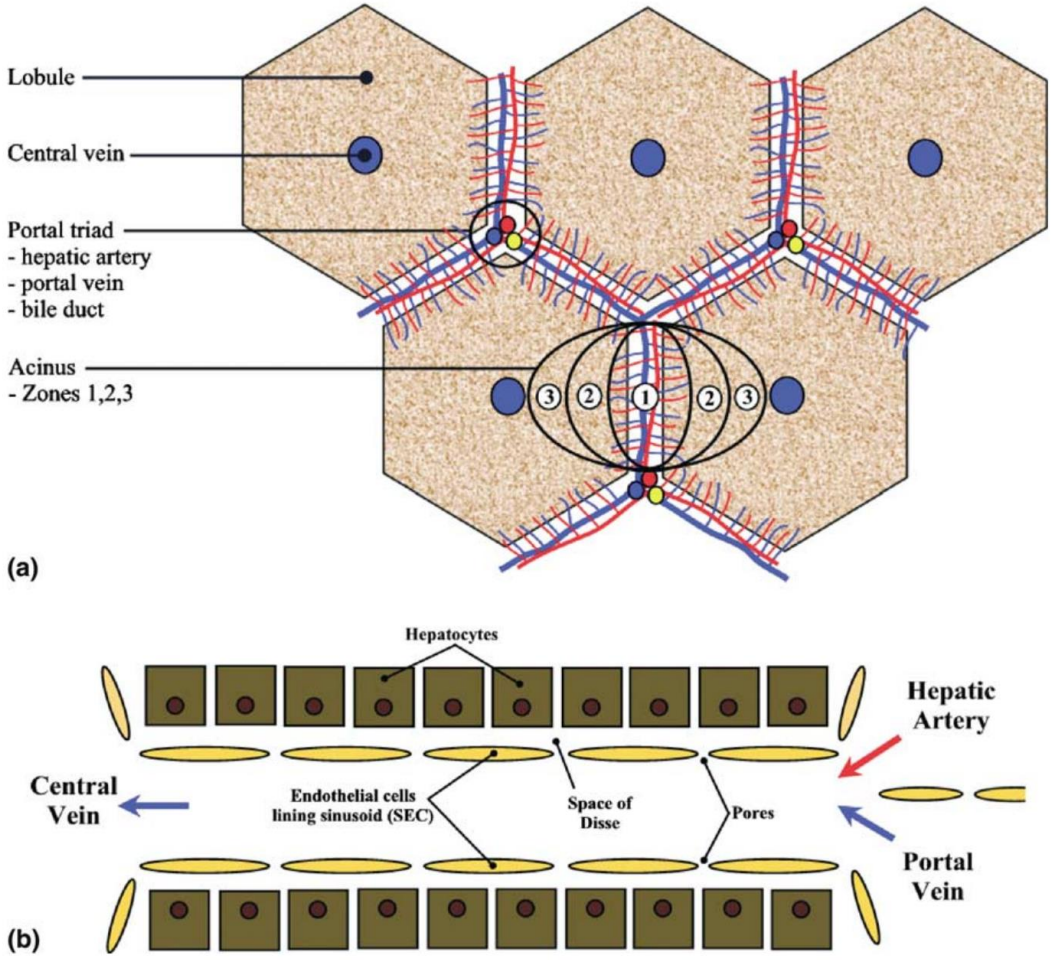
EBMT Handbook 2019

SOS/VOD Time to Onset



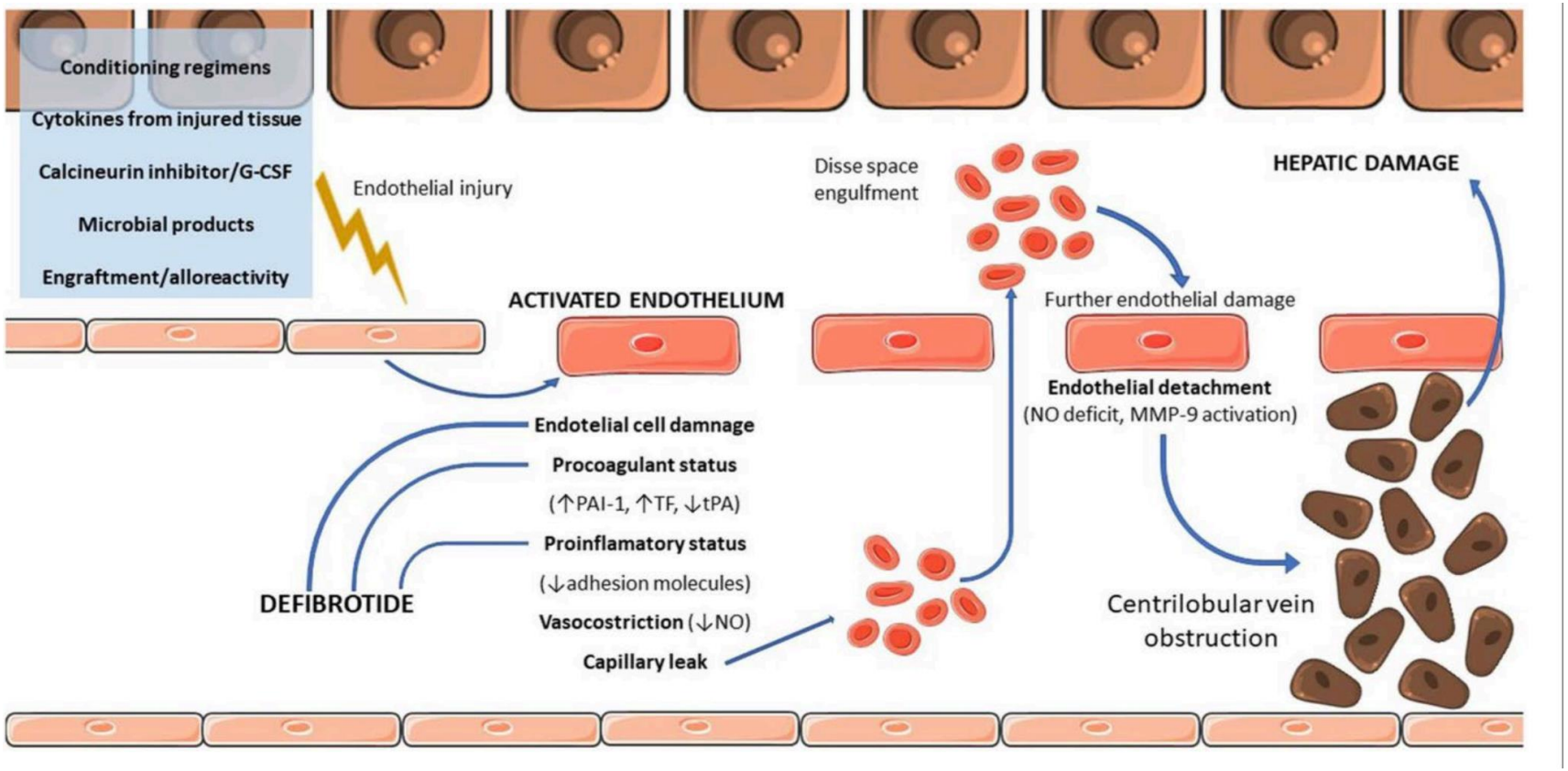
Ruutu et al Bone Marrow Transplantation 2023

Physiopathology I



Coppell et al Blood Reviews (2003)

Physiopathology II



Bonifazi et al. Frontiers 2020

EBMT Diagnostic criteria for SOS/VOD

Classical SOS/VOD	Late onset SOS/VOD
In the first 21 days after HSCT	>21 days after HSCT
Bilirubin ≥ 2 mg/dL AND two of the following criteria must be present: • Painful hepatomegaly • Weight gain >5% • Ascites	Classical VOD/SOS beyond day 21 OR Histologically proven SOS/VOD OR Two or more of the following criteria must be present: • Bilirubin ≥ 2 mg/dL (or 34 µmol/L) • Painful hepatomegaly • Weight gain > 5% • Ascites AND haemodynamic or/and ultrasound evidence of SOS/VOD

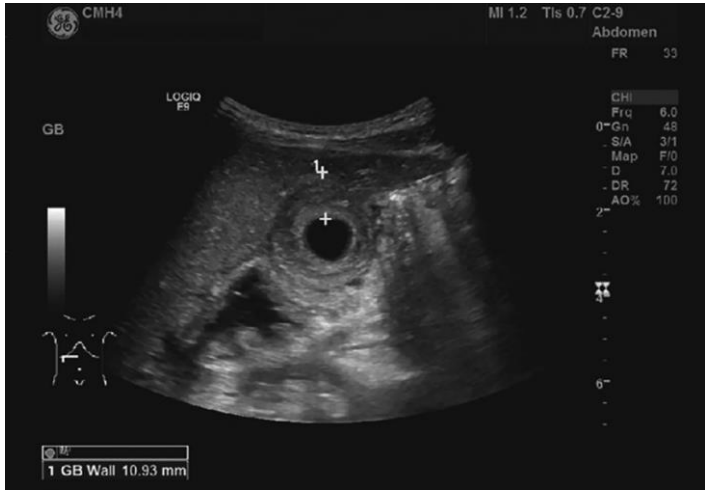
Hyperbilirubinemia no longer mandatory in late onset SOS/VOD

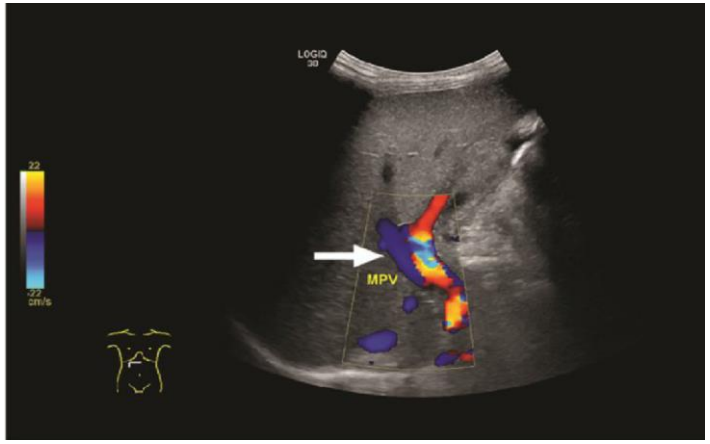
Histological evidence of SOS/VOD remains the gold standard (but not mandatory) for the diagnosis

Transjugular hemodynamic study : HVPG > 10mmHg, Specificity 90%, Sensitivity 60%

Corbacioglu et al. BBMT 2016

Ultrasound features of SOS/VOD





Scoring System
Grayscale ultrasound findings of VOD
1. Hepatomegaly 2. Splenomegaly 3. Gallbladder wall thickening greater than 6 mm 4. Portal vein diameter greater than 8 mm in children and 12 in adults 5. Hepatic vein diameter less than 3 mm 6. Ascites 7. Visualization of para-umbilical vein
Doppler criteria for diagnosis of VOD
1. Flow demodulation in portal vein 2. Decrease in spectral density 3. Reversed portal venous flow or Velocity max less than 10 cm/sec 4. Portal vein Congestion Index 0.1 or greater 5. Hepatic artery resistive index of 0.75 or greater 6. Monophasic flow in hepatic veins 7. Flow demonstrated in para-umbilical vein

Bajwa et al Biology of Blood and Marrow Transplantation 2017
Chan et al Biology of Blood and Marrow Transplantation 2020

Severity Assessment

	Mild*	Moderate*	Severe	Very severe-MOD/MOF**
Time since first clinical symptoms of SOS/VOD* **	> 7 days	5-7 days	≤ 4 days	Any time
Bilirubin (mg/dL) **Bilirubin (µmol/L)**	≥ 2 and < 3 ≥ 34 and <51	≥ 3 and < 5 ≥ 51 and < 85	≥ 5 and < 8 ≥ 85 and < 136	≥ 8 ≥ 136
Bilirubin kinetics			Doubling within 48 hours	
Transaminases	≤ 2 × normal	> 2 and ≤ 5 × normal	> 5 and ≤ 8 × normal	> 8 × normal
Weight increase	< 5%	≥ 5 % and <10%	≥ 5 % and <10%	≥ 10 %
Renal function	<1.2 × baseline at transplant	≥ 1.2 and < 1.5 × baseline at transplant	≥ 1.5 and < 2 × baseline at transplant	≥ 2 × baseline at transplant or other signs of MOD/MOF

SOS/VOD Treatment

Low-moderate severity disease

Supportive care measures : Monitoring, Maintain euvolemia, Paracentesis if necessary.

Avoid hepatotoxic drugs

Methylprednisolone: Used by some authors. Recommended doses not defined.

Severe disease:

Defibrotide (not reimbursed in Belgium)

→For severe VOD : 6.25 mg/kg 4x/d, during 3 weeks

N.S. 26yo male, D+45 post HSCT

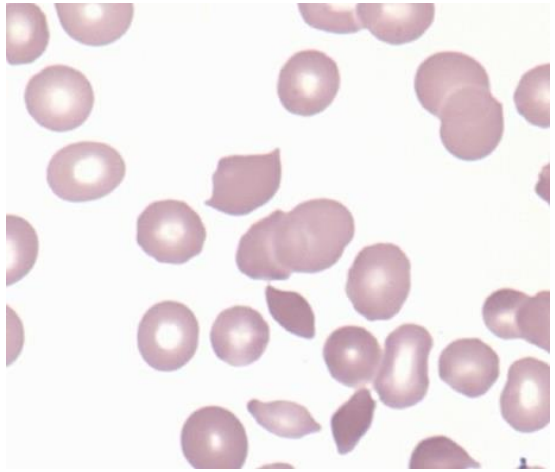
R- Hodgkin Lymphoma, CR2 post Brentuximab – Nivolumab, Haplo-HSCT (father) A+/AB+, CMV+/CMV+.

Conditioning: Thiotepa/Busulfan/Fludarabine

GVHD prophylaxis: PTCy + Ciclosporine/MMF

D+35 aGVHD G2 (Skin 3) → Methylprednisolone 1mg/kg.

D+45: Hb 9.3 g/dl, Ret 160000/mcl, Plt 22.000/µL, Creat 0.78mg/dl**, Schisto 24/1000, LDH 730/mcl, hapto<10**.

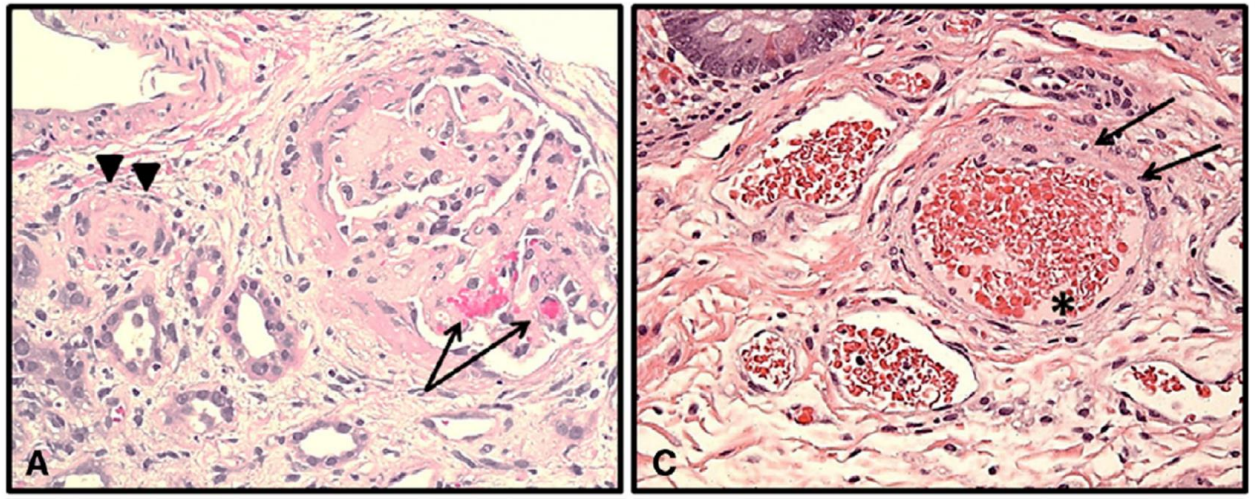


Transplant Associated Thrombotic Microangiopathy (TA-TMA)

More frequent in the first 100 days after transplant.

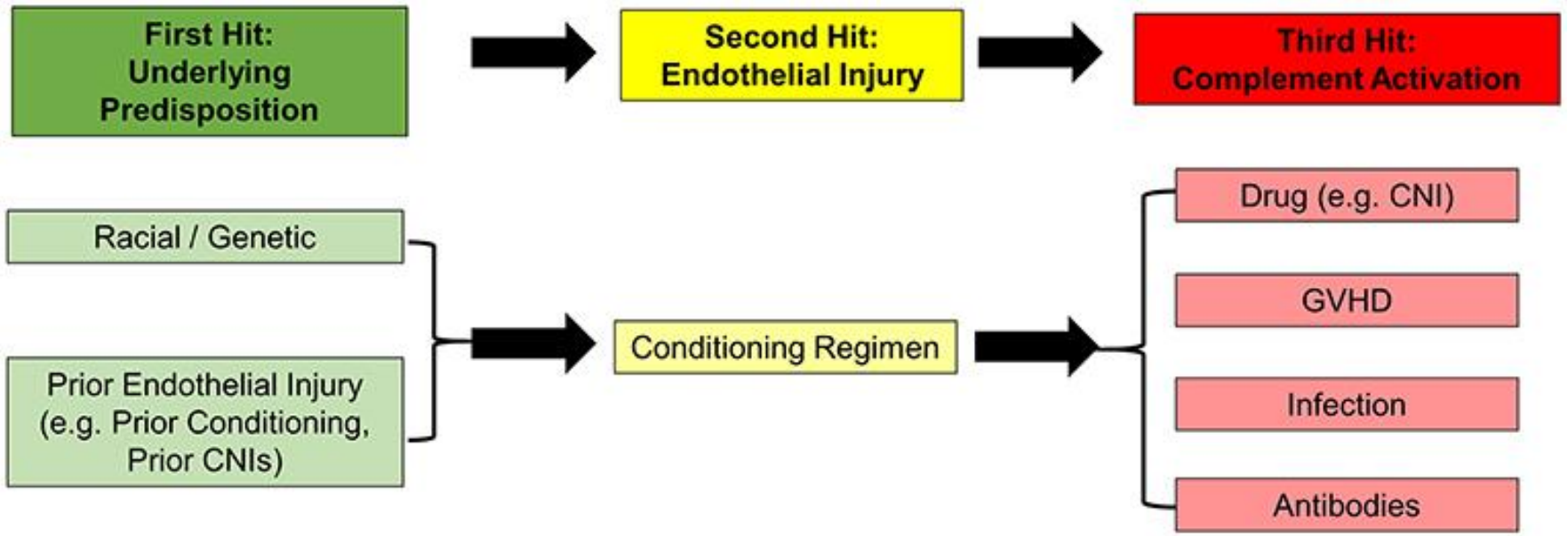
Life-threatening complication

- Microangiopathic haemolytic anaemia
- Consumptive thrombocytopenia
- Microvascular thrombosis with end-organ damage that is associated with highly unfavourable post-HSCT survival.

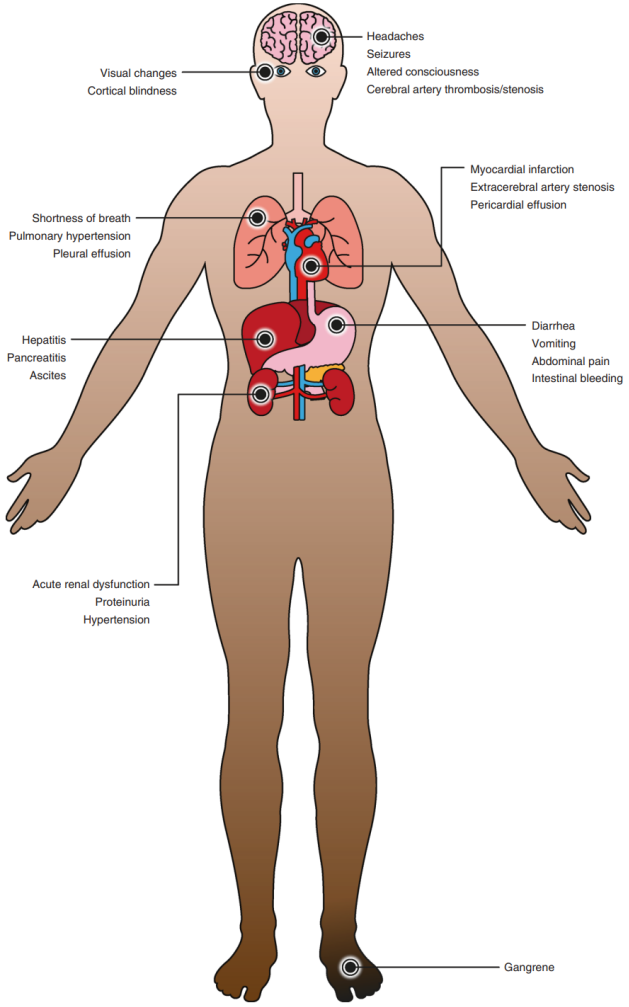


EBMT Handbook 2019
Gavriilaki et al, Exp Hematol Oncol. 2021

Physiopathology: three hits model



Dvorak Front Ped 2019



- **Kidney**

Renal failure, HTA, proteinuria

- **GI tract**

Intestinal bleeding, ischemic colitis

- **CNS**

Seizures, bleeding

- **Cardiopulmonar**

ARDS, bleeding

- **Skin**

Vasculitis, purpura, gangrene

TA-TMA can be limited to the kidney without systemic findings.

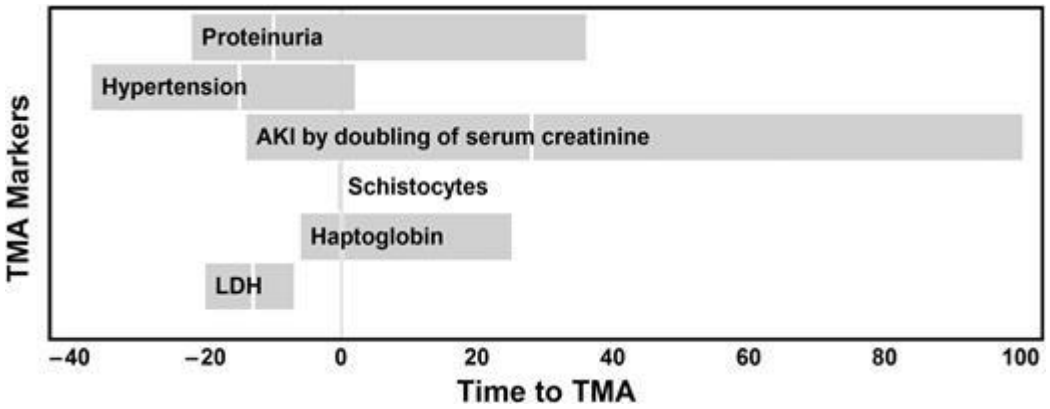
Young et al BMT 2021
Mahmoudjafari et al. BMT 2023
Iordachescu et al Kidney Med. 2023

Diagnosis et prognostic factors

Tissue diagnosis or >4 of the following criteria

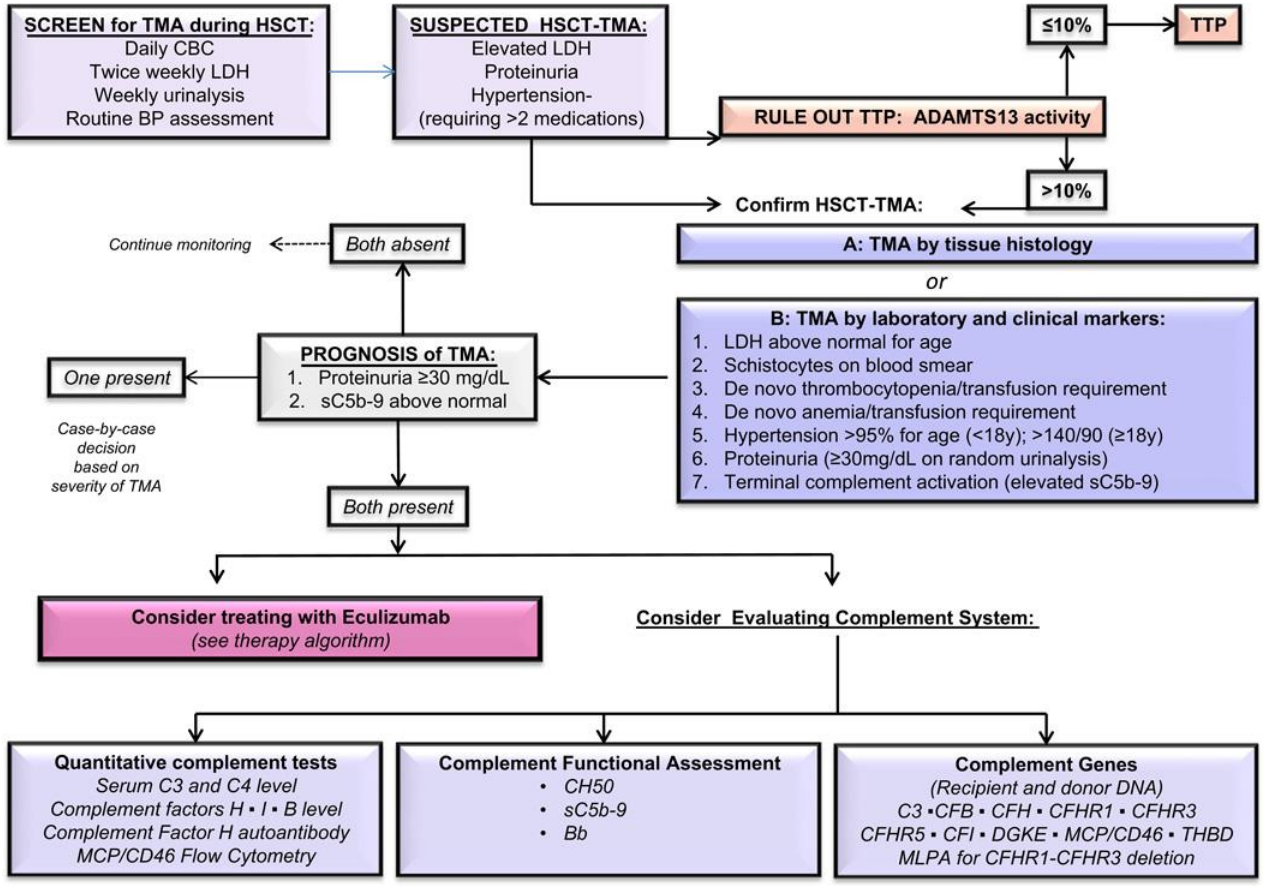
- Increased LDH
- Schistocytes +
- Thrombocytopenia and anaemia worsening
- Arterial Hypertension
- Proteinuria >30mg / dl
- Increased sC5b-9

} Severity Criteria



Jodele et al. Blood. 2014

TA-TMA : Algorithm



Jodele S et al, Blood Rev. 2015

Management

Supportive treatment

Transfusion support

Discontinue causative agents

Adapt immunosuppression (+/-)

Treat factors (GvHD, infections)

Aggressively treat hypertension

Monitor for organ injury

TMA targeted therapy

Complement blocking agents

Other therapies: Defibrotide
Plasma exchange Rituximab

Chemo-radiotherapy related direct toxicities

- Mucositis
- Hemorrhagic cystitis
- Others (hepatic cytolysis, renal failure....)

Mucositis

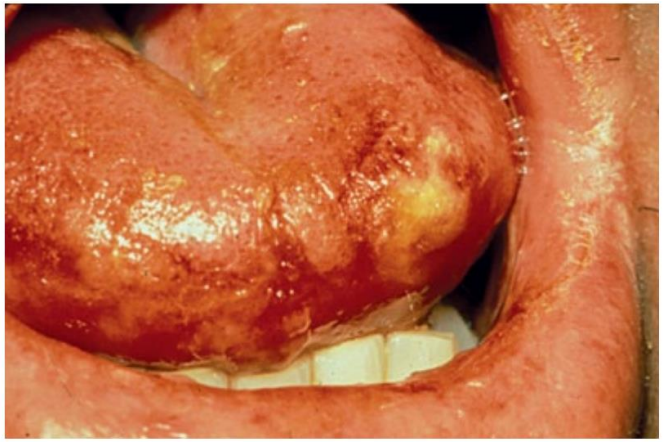
Oral mucositis: mouth ulcers/erythema

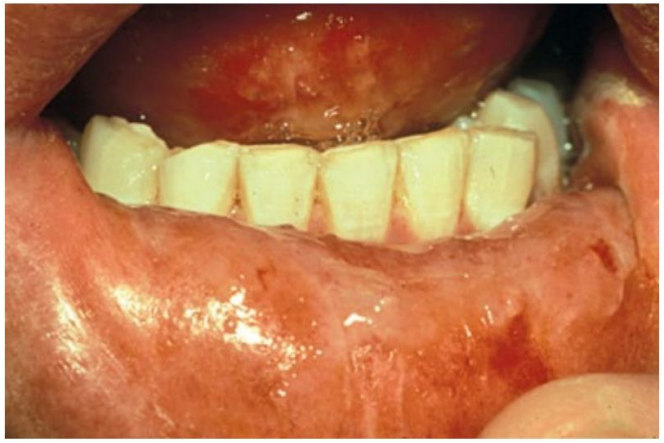
Gastro-intestinal mucositis: diarrhea, abdominal pain, constipation

Common complication of HSCT (80% of patients with high dose chemo)

Onset: 5-7 days post HSCT, peaks D+ 9-13

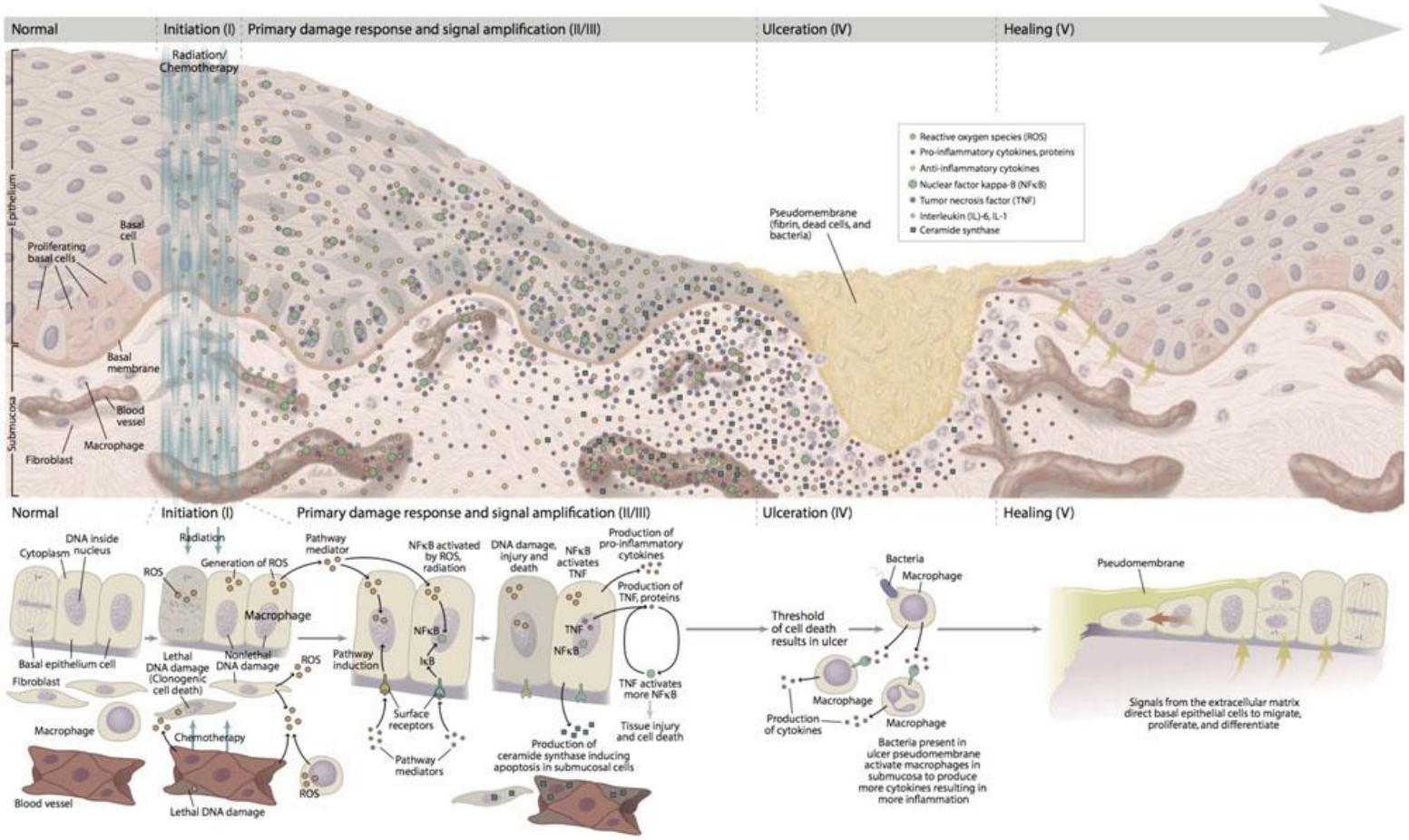
Difficult to treat, highly painful and poor-responsive to analgesics





Grade	Description
Mild	
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
Severe	
III (severe)	Oral ulcers, liquid diet only
IV (life-threatening)	Oral alimentation impossible

Physiopathology



Cinausero Front. Pharmacol. 2017

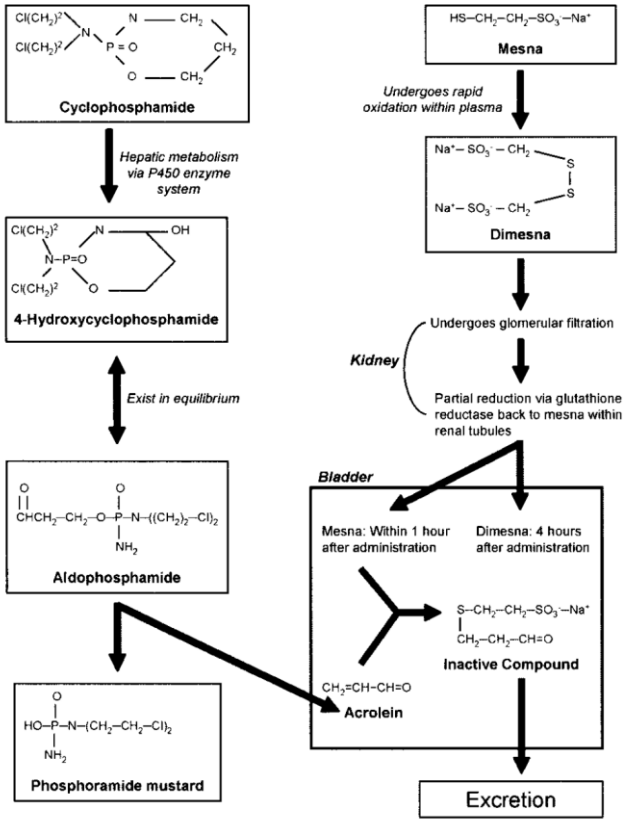
Hemorrhagic Cystitis

Early < 1 week after HSCT

Direct toxic effect of drug metabolites or RT on the bladder mucosa.

(Cyclophosphamide /acroleine)

Prevention: hyperhydratation + MESNA



Monach et al Art rhum 2010

A. J. 42 yo, D+10 post HSCT

Hb 8.5 gr/dl, WBC 100/mcl, Plt 21000/mcl

MSD-HSCT for AML in CR1, Conditioning FluBu4.

Neutropenic fever D+5 → Cefepime

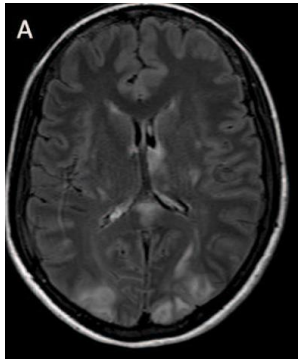
D+10

Hallucinations

Clinical examination : BP 170/100, FC 100, T 36.9°C . Neuro: no focal deficit, hallucinations +, confusion +, tremor.

EEG: encephalopathy, aspecific

Brain MRI: T2 Flair, posterior hypersignal



Neurologic complications after HSCT

Drug related

- Antibiotics
- Calcineurin inhibitors
- Cytotoxic agent

Vascular

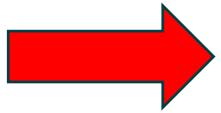
- Hemorrhage/stroke
- Thrombosis

Metabolic

- Hepatic encephalopathy
- Uremic encephalopathy

Infectious

- Viral infections
- Bacterial/fungal infections



Extensive work-up

- EEG
- Cerebral MRI
- Lumbar Puncture with wide microbiological analysis

Posterior Reversible Encephalopathy Syndrome (PRES)

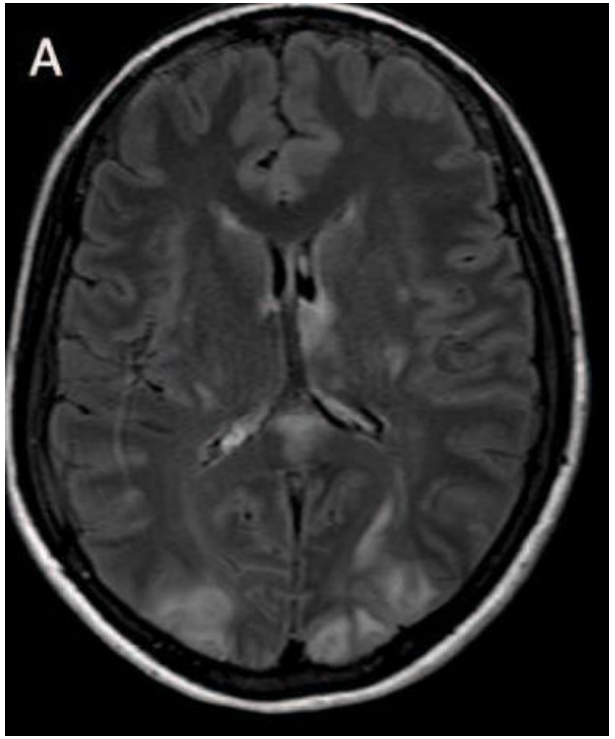
Physiopathology:

Endothelial damage by calcineurin inhibitors

Vasogenic edema involving the parietal and occipital white matter

Clinical: HTA + encephalopathy, visual disturbances, Headache, Seizures.

MRI: bilateral areas of white matter edema in the posterior cerebral hemispheres



PRES Management

Blood pressure management

Lower the diastolic pressure to approximately 100 to 105 mmHg in 2-6h

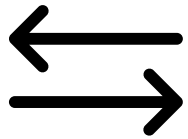
Seizure management

Antiepileptic drugs and EEG monitoring

Discontinuation of immunosuppressive therapy

Reduction in drug dose or prompt removal of the cytotoxic or immunosuppressive drug

Tacro>>Sirolimus



Vaughan Lancet. 2000
Hauben Pharmacotherapy. 1996

Late complications of HSCT

Secondary neoplasia

i. Therapy related myeloid neoplasia after auto-HSCT

Radiation/alkylating treatment

ii. Donor cell leukemia (DCL)

Extremely rare and are either transmitted from the donor or newly transformed in the host.

iii. Second solid neoplasia (SSN) after auto-HSCT and allo-HSCT

Non-squamous second solid cancers (breast, thyroid, brain, etc.) are strongly related to local radiation or TBI and occur with long delay after HSCT.

Squamous cell carcinoma of the skin, the oral cavity, and the pharynx is related with chronic GVHD and can occur early after HSCT.

Solid cancers

Breast cancer: 11% at 25 years

Thyroid cancer: SIR 3.2 compared to general population

Basal Cell Carcinoma: 6.5% at 20 years

Squamous cell carcinoma of the skin: 3.4% at 20 years

Should be treated as de novo cancers of the same type

Friedman et al. (2008)
Cohen et al. (2007)
Leisenring et al. (2006)
Curtis et al (2005)

Screening for secondary solid tumor

Skin	*All patients* Encouraged to • Perform regularly genital/testicular and skin self-examination • To avoid unprotected UV skin exposure Skin examination by dermatologist every 1–2 years *Patients at risk* More frequent examination by dermatologist • After first skin cancer • Patients with chronic skin GvHD
Oral cavity and pharynx	*All patients* Examination during annual control *Patients at risk* Annual control by specialist if severe oral and pharynx GvHD Histology in case of suspicious lesion
Thyroid	*All patients* Annual thyroid palpation to identify suspicious thyroid nodules *Patients at risk* (patients at risk after TBI or local radiation) Regular thyroid ultrasound Fine needle aspiration in case of a suspicious nodule
Breast	*All patients* Discuss breast self-examination with their physician *Patients at risk* Screening mammography every 1 to 2 years starts at the age of 25 or 8 years after radiation, whichever occurs later, but not later than age of 40 years
Cervix	*All patients* Screening with pap smears every 1–3 years in women older than 21 or within 3 years of initial sexual activity, whichever occurs earlier
Lung	*All patients* Encouraged to avoid smoking and passive tobacco exposure *Patients at risk* Patients at risk (high-dose busulfan conditioning and smoking), chest CT
Liver	*Patients at risk* Patients with known HCV infection should be assessed for fibrosis/cirrhosis of the liver 8–10 years after HSCT (biopsy; fibroscan)
Colorectal	*All patients* Screening should start at age 50 in absence of a family history (first-degree relative diagnosed with colorectal cancer before age 60): annual fecal occult blood testing, sigmoidoscopy every 5 years, with fecal occult testing every 3 years, or colonoscopy every 10 years
Prostate	*All patients* No specific recommendations

EBMT Handbook 2019

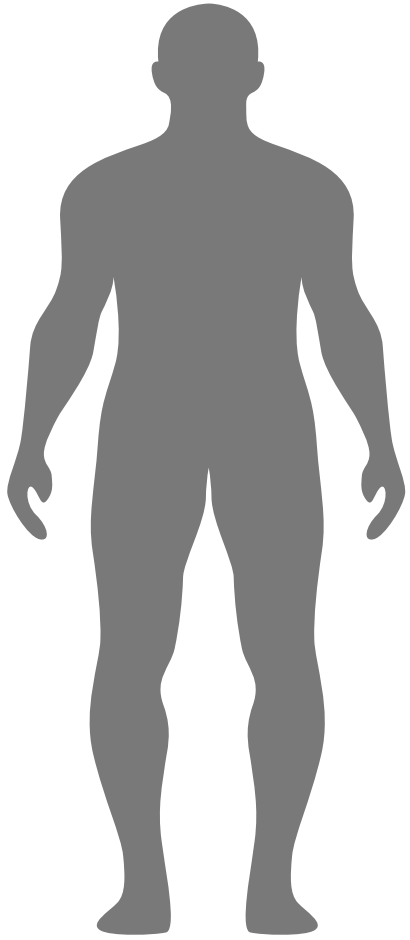
Organ specific late complications

Neuropsychological/cognitive deficiency
Polyneuropathy
Leukoencephalopaty

Cataract <TBI, steroids
cGVHD-sicca syndrome
Microvascular retinopathy

GVHD
Iron overload

Chronic kidney disease
Bladder dysfunction



Hypoparathyroidism
Hypothyroidism
Hypogonadism - infertility

Idiopathic pneumonia syndrome
cGVHD-obliterans bronchiolitis
Infections

Hyperlypemia, HTA, diabetes
Ischemic heart disease
Arrythmias

Osteopenia/osteoporosis
Avascular necrosis

Summary recommendations for screening and prevention of late complications in long-term HCT survivors

Tissues/organs	Late Complications	General Risk Factors	Monitoring Tests	Monitoring Tests and Preventive Measures In All HCT Recipients	Monitoring Tests and Preventive Measures In Special Populations
Immune system	- Infections	- Donor source - HLA disparity - T-cell depletion - GVHD - Prolonged immunosuppression - Venous access devices	- CMV antigen or PCR in patients at high risk for CMV reactivation	- PCP prophylaxis for initial 6 months after HCT - Immunizations post-transplant according to published guidelines - Administration of antibiotics for endocarditis prophylaxis according to American Heart Association guidelines	- Patients with cGVHD: Antimicrobial prophylaxis targeting encapsulated organisms and PCP for the duration of immunosuppressive therapy - Patients with cGVHD: Screening for CMV reactivation should be based on risk factors, including intensity of immunosuppression.
Ocular	- Cataracts - Sicca syndrome - Microvascular retinopathy	- TBI/radiation exposure to head and neck - Corticosteroids - GVHD	- Ophthalmologic exam	- **Routine clinical evaluation at 6 months and 1 year after HCT and at least yearly thereafter** - Ophthalmologic examination with measurement of visual acuity and fundus examination at 1 year after HCT, subsequent evaluation based on findings and risk-factors - Prompt ophthalmologic examination in patients with visual symptoms	- Patients with cGVHD: Routine clinical evaluation, and if indicated, ophthalmologic examination more frequently
Oral	- Sicca syndrome - Caries	- GVHD - TBI/radiation exposure to head and neck	- Dental assessment	- Education about preventive oral health practices - Clinical oral assessment at 6 months and 1 year after HCT and at least yearly thereafter with particular attention to intra-oral malignancy evaluation - Dental assessment at 1 year after HCT and then at least yearly thereafter	- Pediatric recipients: Yearly assessment of teeth development - Patients with cGVHD: Consider more frequent oral and dental assesments with particular attention to intra-oral malignancy evaluation
Respiratory	- Idiopathic pneumonia syndrome - Bronchiolitis obliterans syndrome - Cryptogenic organizing pneumonia	- TBI/radiation exposure to chest - GVHD - Infectious agents - Allogeneic HCT - Busulfan exposure	- PFT's - Radiologic studies (e.g. chest X-ray, CT scan)	- Routine clinical evaluation at 6 months and 1 year after HCT and at least yearly thereafter - Assessment of tobacco use and couselling against smoking - PFT's and focused radiologic assessment for allogeneic HCT	- Patients with cGVHD: Some experts recommend earlier and more frequent clinical evaluation and PFT's

Majhail et al. BMT 2012

Tissues/organs	Late Complications	General Risk Factors	Monitoring Tests	Monitoring Tests and Preventive Measures In All HCT Recipients	Monitoring Tests and Preventive Measures In Special Populations
	- Sino-pulmonary infections			recipients with symptoms or signs of lung compromise	
Cardiac and vascular	- Cardiomyopathy - Congestive heart failure - Arrhythmias - Valvular anomaly - Coronary artery disease - Cerebrovascular disease - Peripheral arterial disease	- Anthracycline exposure - TBI/radiation exposure to neck or chest - Older age at HCT - Allogeneic HCT - Cardiovascular risk-factors before/after HCT - Chronic kidney disease - Metabolic syndrome	- Cumulative dose of anthracyclines - Echocardiogram with ventricular function, ECG in patients at risk and in symptomatic patients - Fasting lipid profile (including HDL-C, LDL-C and triglycerides) - Fasting blood sugar	- Routine clinical assessment of cardiovascular risk factors as per general health maintenance at 1 year and at least yearly thereafter - Education and counseling on "heart" healthy lifestyle (regular exercise, healthy weight, no smoking, dietary counseling) - Early treatment of cardiovascular risk factors such as diabetes, hypertension and dyslipidemia - Administration of antibiotics for endocarditis prophylaxis according to American Heart Association guidelines	
Liver	- GVHD - Hepatitis B - Hepatitis C - Iron overload	- Cumulative transfusion exposure - Risk factors for viral hepatitis transmission	- LFT's - Liver biopsy - Serum ferritin - Imaging for iron overload (MRI or SQUID)	- LFT's every 3–6 months in the first year, then individualized, but at least yearly thereafter - Monitor viral load by PCR for patients with known hepatitis B or C, with liver and infectious disease specialist consultation - Consider liver biopsy at 8–10 years after HCT to assess cirrhosis in patients with chronic HCV infection - Serum ferritin at 1 year after HCT in patients who have received RBC transfusions; consider liver biopsy or imaging study for abnormal results based on magnitude of elevation and clinical context; subsequent monitoring is suggested for patients with elevated LFT's, continued RBC transfusions, or presence of HCV infection	
Renal and genitourinary	- Chronic kidney disease - Bladder dysfunction - Urinary tract infections	- TBI - Drug exposure (e.g. calcineurin inhibitors, amphotericin, aminoglycosides) - CMV - Hemorrhagic cystitis	- Urine protein - Serum creatinine - BUN	- Blood pressure assessment at every clinic visit, with aggressive hypertension management - Assess renal function with BUN, creatinine and urine protein at 6 months, 1 year and at least yearly thereafter	

Majhail et al. BMT 2012

Tissues/organs	Late Complications	General Risk Factors	Monitoring Tests	Monitoring Tests and Preventive Measures In All HCT Recipients	Monitoring Tests and Preventive Measures In Special Populations
				- Consider further workup (kidney biopsy or renal ultrasound) for for further workup of renal dysfunction as clinically indicated	
Muscle and connective tissue	- Myopathy - Fascitis/scleroderma - Polymyositis	- Corticosteroids - GVHD	- Evaluate ability to stand from a sitting position - Clinical evaluation of joint range of motion	- Follow general population guidelines for physical activity - Frequent clinical evaluation for myopathy in patients on corticosteroids	- Patients with cGVHD: Physical therapy consultation in patients with prolonged corticosteroid exposure, fascitis or scleroderma - Patients with cGVHD: Frequent clinical evaluation by manual muscle tests or by assessing ability to go from sitting to standing position for patients on prolonged corticosteroids
Skeletal	- Osteopenia/osteoporosis - Avascular necrosis	- Inactivity - TBI - Corticosteroids - GVHD - Hypogonadism - Allogeneic HCT	- Dual photon densitometry - MRI to evaluate patients with joint symptoms	- Dual photon densitometry at 1 year for adult women, all allogeneic HCT recipients and patients who are at high risk for bone loss; subsequent testing determined by defects or to assess response to therapy - Physical activity, vitamin D and calcium supplementation to prevent loss of bone density	- Patients with cGVHD: Consider dual photon densitometry at an earlier date in patients with prolonged corticosteroid or calcineurin inhibitor exposure.
Nervous system	- Leukoencephalopathy - Late infections - Neuropsychological and cognitive deficits - Calcineurin neurotoxicity - Peripheral neuropathy	- TBI/radiation exposure to head - GVHD - Exposure to fludarabine - Intrathecal chemotherapy	-	- Clinical evaluation for symptoms and signs of neurologic dysfunction at 1 year and yearly thereafter - Diagnostic testing (e.g., radiographs, nerve conduction studies) for those with symptoms or signs	- Pediatric recipients: Annual assessment for congnitive development milestones
Endocrine	- Hypothyroidism - Hypoadrenalism - Hypogonadism - Growth retardation	- TBI/radiation exposure (e.g. head and neck, CNS) - Corticosteroids - Young age at HCT - Chemotherapy exposure	- Thyroid function tests - FSH, LH, testosterone - Growth velocity in children	- Thyroid function testing yearly post-HCT, or if relevant symptoms develop - Clinical and endocrinologic gonadal assessment for post-pubertal women at 1 year, subsequent followup based on menopausal status - Gonadal function in men, including FSH, LH and testosterone, should be assessed as warranted by symptoms	- Pediatric recipients: Clinical and endocrinologic gonadal assessment for pre-pubertal boys and girls within 1 year of transplant, with further followup as determined in consultation with a pediatric endocrinologist - Pediatric recipients: Monitor growth velocity in children

Majhail et al. BMT 2012

Tissues/organs	Late Complications	General Risk Factors	Monitoring Tests	Monitoring Tests and Preventive Measures In All HCT Recipients	Monitoring Tests and Preventive Measures In Special Populations
					annually; assessment of thyroid, and growth hormone function if clinically indicated - Patients with cGVHD: Slow terminal tapering of corticosteroids for those with prolonged exposure - Patients with cGVHD: Consider stress doses of corticosteroids during acute illness for patients who have received chronic corticosteroids
Mucocutaneous	- Cutaneous sclerosis - Genital GVHD	- GVHD - TBI/radiation exposure to pelvis	- Pelvic exam	- Counsel patients to perform routine self exam of skin and avoid excessive exposure to sunlight without adequate protection - Annual gynecologic exam in women to detect early involvement of vaginal mucosa by GVHD	- Patients with cGVHD and TBI recipients: Consider more frequent gynecologic evaluation based on clinical symptoms
Second cancers	- Solid tumors - Hematologic malignancies - PTLD	- GVHD - TBI/radiation exposure - T-cell depletion - Exposure to alkylating agents or etoposide	- Mammogram - Screening for colon cancer (e.g. colonscopy, sigmoidoscopy, fecal occult blood testing) - Pap smear	- Counsel patients about risks of secondary malignancies annually and encourage them to perform self exam (e.g. skin, testicles/genitalia) - Counsel patients to avoid high risk behaviors (e.g. smoking) - Follow general population recommendations for cancer screening	- Patients with cGVHD: Clinical and dental evaluation with particular attention towards oral and pharyngeal cancer - TBI and chest irradiation recipients: Screening mammography in women starting at age 25 or 8 years after radiation exposure, whichever occurs later but no later than age 40
Psychosocial and sexual	- Depression - Anxiety - Fatigue - Sexual dysfunction	- Prior psychiatric morbidity - Hypogonadism	- Psychological evaluation	- Clinical assessment throughout recovery period, at 6 months, 1 year and annually thereafter, with mental health professional counseling recommended for those with recognized deficits - Encouragement of robust support networks - Regularly assess level of spousal/ caregiver psychological adjustment and family functioning	

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Tissues/organs	Late Complications	General Risk Factors	Monitoring Tests	Monitoring Tests and Preventive Measures In All HCT Recipients	Monitoring Tests and Preventive Measures In Special Populations
				- Query adults about sexual function at 6 months, 1 year and at least annually thereafter	
Fertility	- Infertility	- TBI/radiation exposure - Chemotherapy exposure	- FSH, LH levels	- Consider referral to appropriate specialists for patients who are contemplating a pregnancy or are having difficulty conceiving - Counsel sexually active patients in the reproductive age group about birth control post-HCT	
General health				- Recommended screening as per general population (see text)	

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Take home messages

•**Vigilance is Key**: Complications post-HSCT can be life-threatening if not promptly recognized; maintaining a high suspicion alert is crucial.

•**Comprehensive Evaluation**: Extensive work-up is often necessary to identify complications early on.

•**Infection Prevention**: Early intervention is vital in cases of viral reactivation (CMV, EBV)

•**Endothelial Complications**: Remain vigilant for endothelial issues in transplant recipients, emphasizing the need for robust supportive care.

•**Late Complications**: Secondary cancers and different organ diseases may arise later on, necessitating a holistic long-term follow-up approach for HSCT patients.

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