BHS Training course 2013-2015
Seminar 6
Stem Cell Transplantation

Complications other than GVHD

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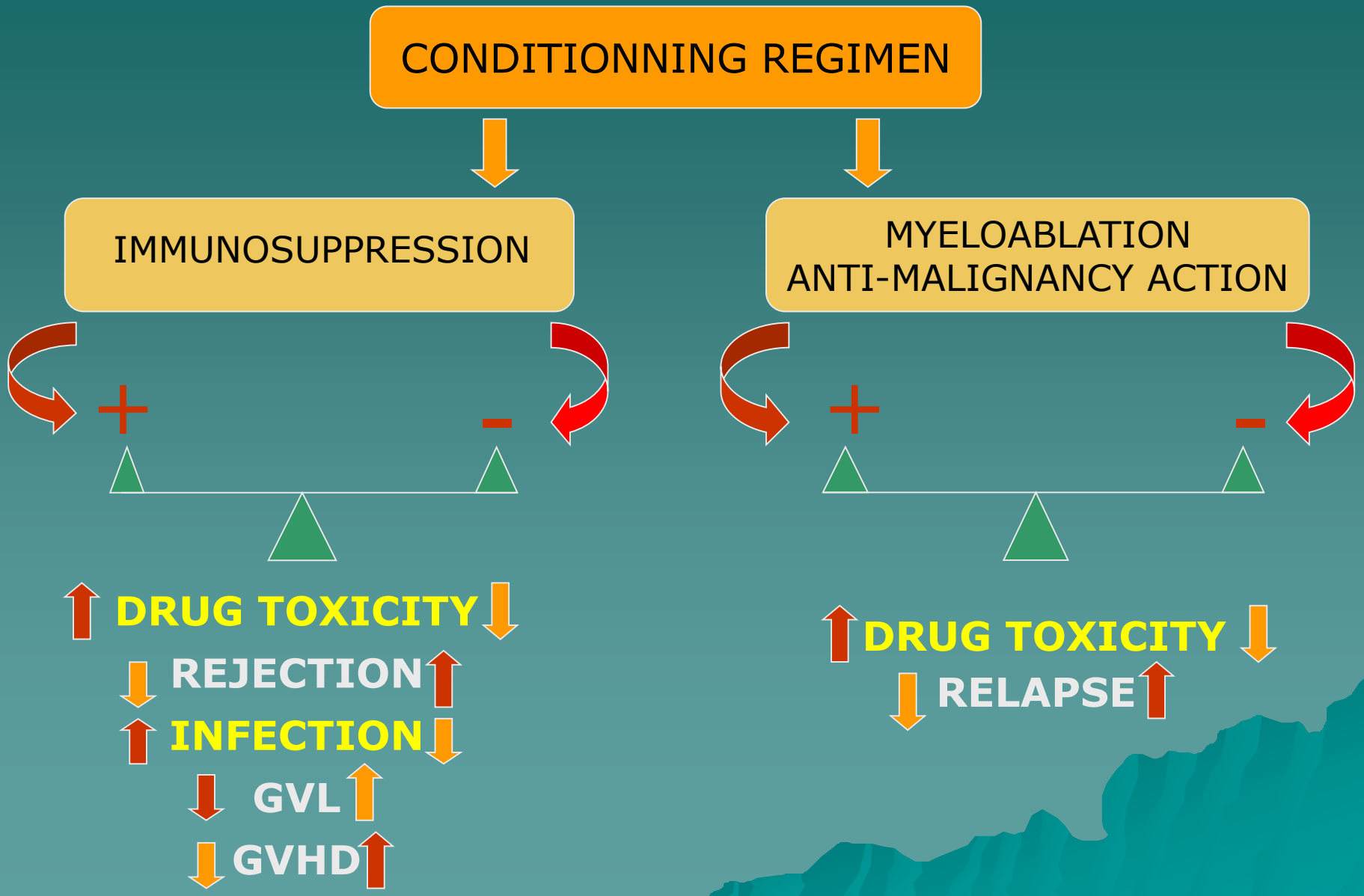
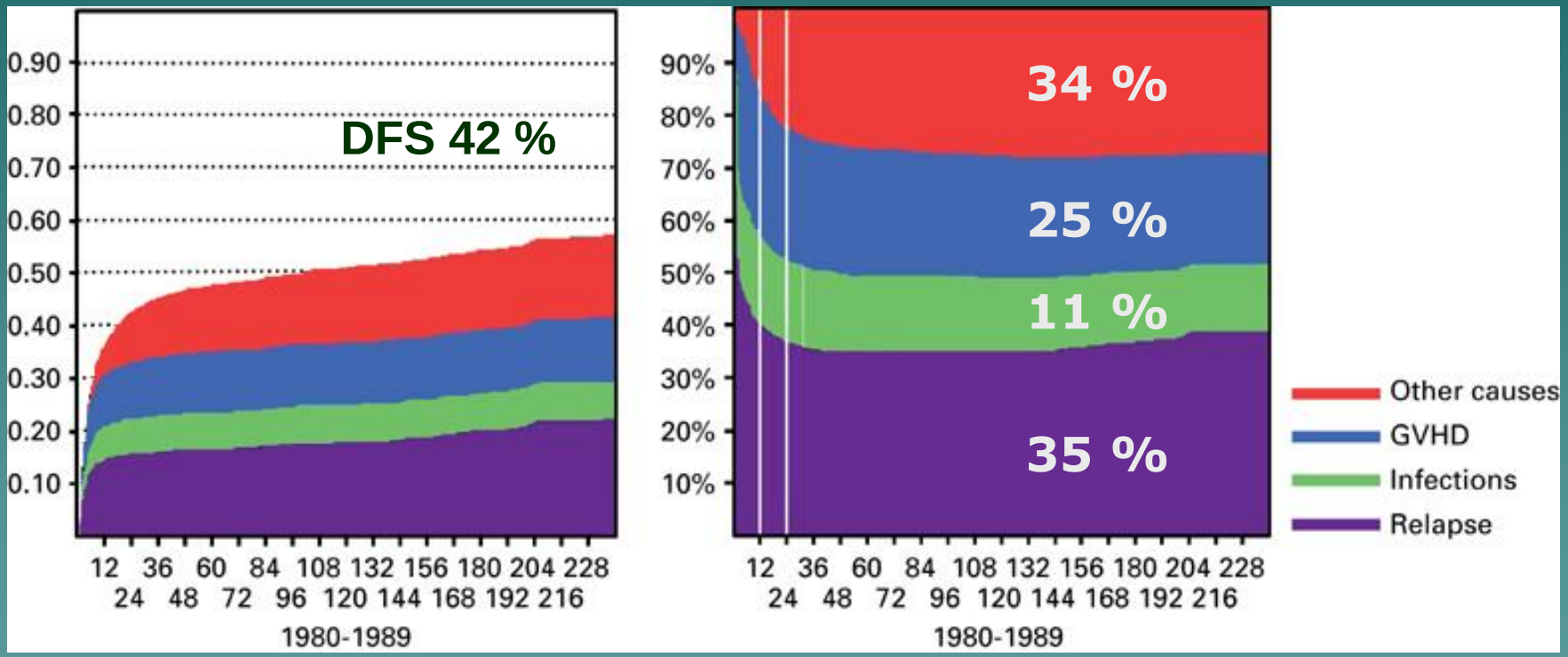
Early complications of HSCT

- Direct action of chemo-radiotherapy
  - Nausea, vomiting, diarrhea, alopecia,pain
  - Mucositis
  - Haemorrhagic cystitis
  - Idiopathic pneumonia syndrome
- Vascular Endothelium syndrome
  - VOD, CLS, TAM, ES, DAH,
- Drug Toxicity (immunosupressors, Antibiotics)
- Infections
- Immune complications (GVHD)

Early toxicities: action of Chemo-radiotherapy



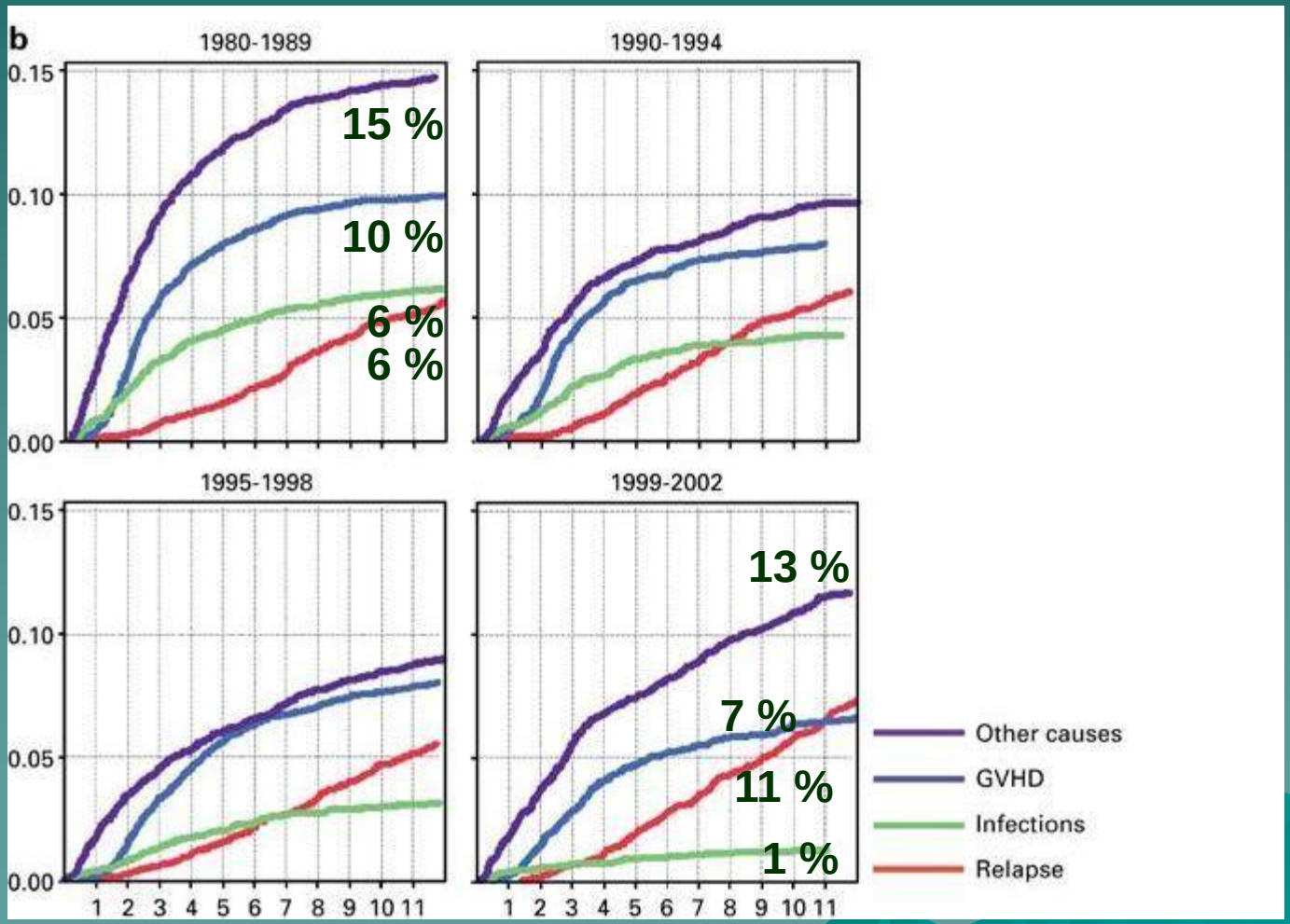
Causes of Death after Allo-HSCT up to 20 years



A Gratwohl, Bone Marrow Transplantation (2005)

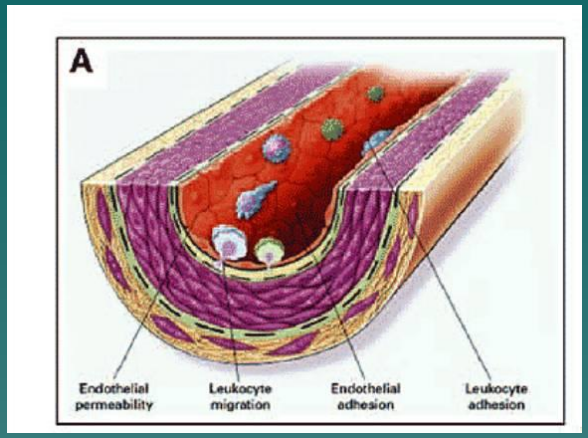
Trends over time, Death at 12 months

OS at 5y has increased from 52% to 62%
Mainly infection decreased from 36% to 26%



A Gratwohl, Bone Marrow Transplantation (2005)

Vascular Endothelium



Input Signals → Output Signal Adaptive Response → Output Signal Dysfunction

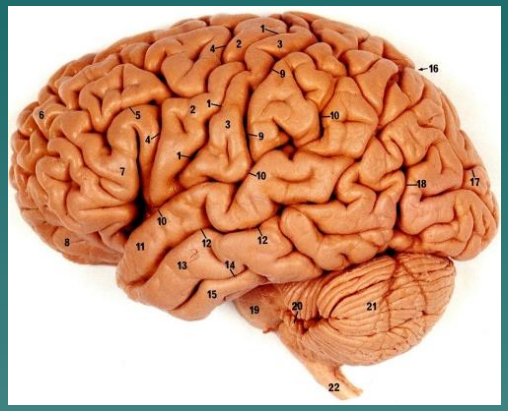
-Cell interaction
-Soluble mediators
-Oxygenation
-Hemodynamic
-Temperature, pH

-Vasomotor tone
-Permeability
-Haemostatic balance
-Inflammatory response
-Cell proliferation & survival

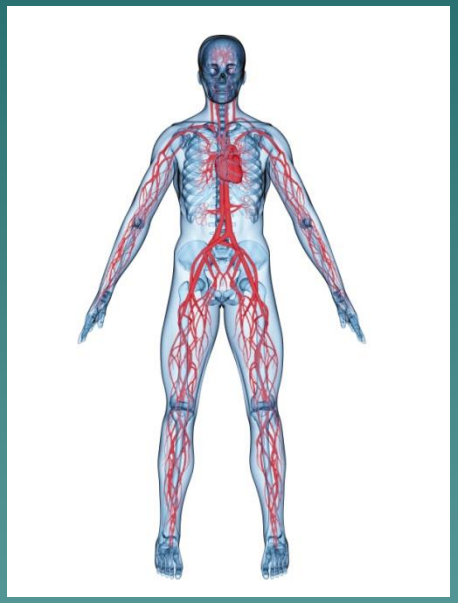
- Cell swelling
- Loss of mitochondria
- Apoptosis
- MHC antigen presentation
- Procoagulant phenotype
- Increased permeability
- ↑Leukocyte trafficking
- inflammatory mediators

BASAL **ACTIVATION** **DISEASE**

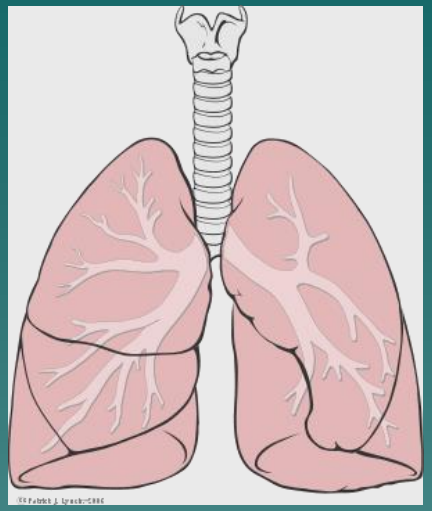
Organs Dysfunction



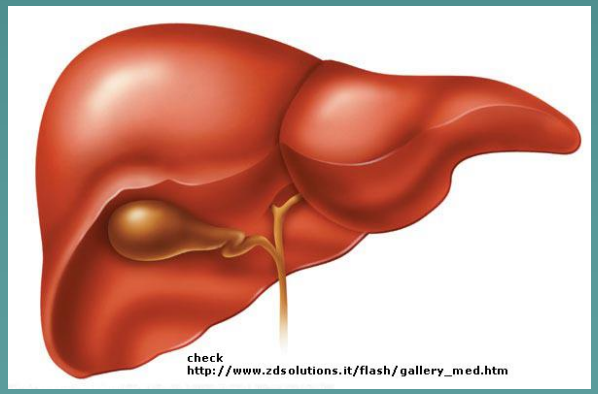
TAM-ES



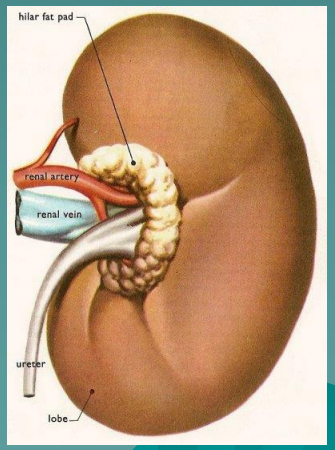
TAM
ES - CLS



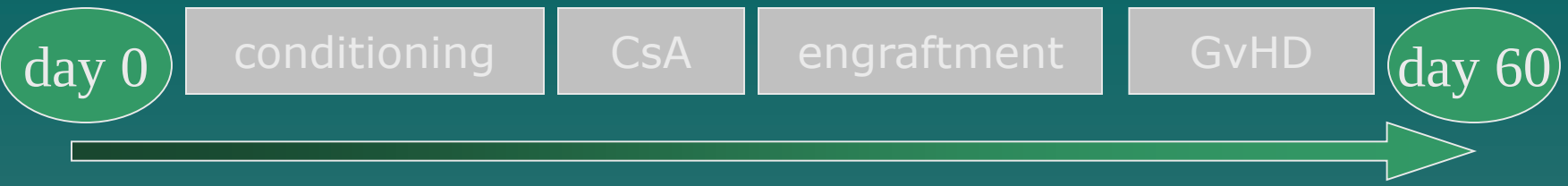
DAH



VOD



TAM



veno-occlusive disease

capillary leak syndrome

BMT associated thrombotic microangiopathy

diffuse alveolar haemorrhage

idiopathic pneumonia syndrome

engraftment syndrome

Overlapping clinical manifestations

MODS

Capillary Leak Syndrome (CLS)

- First 15 days after transplant
- 10-50 %

- Weight gain>3% in 24h00 , generalised oedema (ascite, pleural effusion, pericarditis)

  (hypotension, renal insuffiency and hypo-albuminemia)

- No treatment, poor response to furosemide and steroids.
- Risk factors: growth factors, high pre-HSCT treatment, unrelated or mismatched transplant.
- Mortality rate: High: 8%-40%

Engraftment Syndrome (ES)

- Massive release of pro-inflammatory cytokine (tissue injuries by conditionning and neutrophil recovery)
- Frequency: 7%-50%
- ES should occur within 96 h of engraftment (neutrophil count of 500/ l for 2 consecutive days).

- High fever, skin rash, lung infiltrates (diarrhoea, weight gain, liver, kidney, CNS dysfunction)

- Risk factors: Growth factors, PBSCT.
- Treatment: methylPDN 2mg/KG for one week and rapid tapering
- Mortality rate: 10%

Engraftment Syndrome (ES) Clinical criteria

Major criteria

- Temperature of 38.3˚ C with no identifiable infectious etiology.
- Erythrodermatous rash involving more than 25% of body surface area and not attributable to a medication.
- Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates consistent with this diagnosis, and hypoxia.

Minor criteria

- Hepatic dysfunction with either total bilirubin >2 mg/dl or transaminase levels two times normal.
- Renal insufficiency (serum creatinine of two times baseline).
- Weight gain 2.5% of baseline body weight.
- Transient encephalopathy unexplainable by other causes.

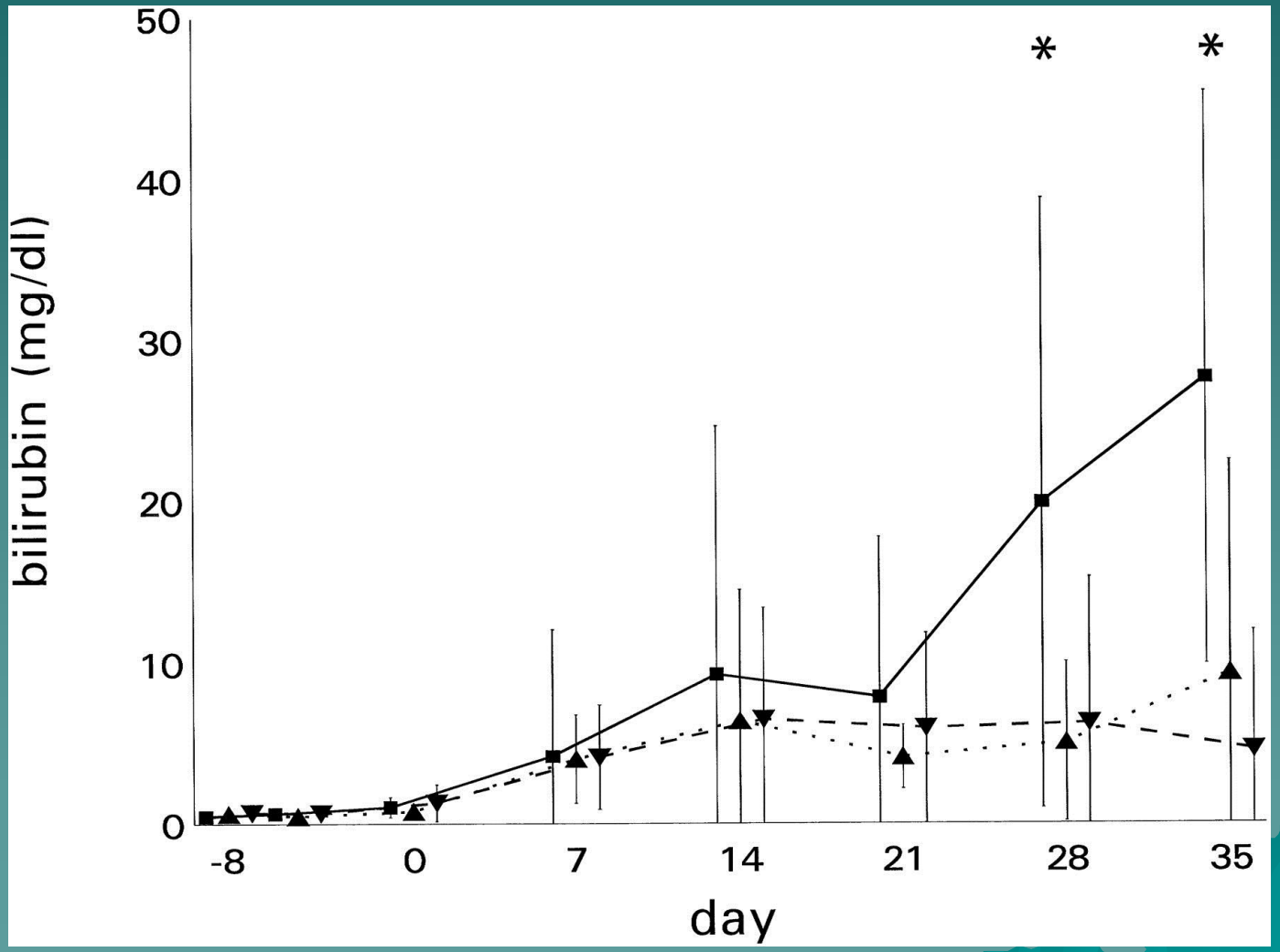
LIVER

Common causes of elevated liver enzymes in the post SCT period

- Side effects of drugs (Methotrexate, Cyclosporine-A, azolium,)
- Infections (bacterial, fungal, viral)
- VOD
- aGVHD
- Relapse of malignancy
- Parenteral nutrition
- Constrictive pericarditis and right congestive heart failure

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Development of Hyperbilirubinemia in BMT recipients.



VOD

GVHD

Other

Salat C et al. Blood 1997;89:2184-2188

Hepatic Veno Occlusive Disease (VOD)

1) Seattle criteria

Presence, before day 30 after transplant, of at least two of the following features:

- 1. jaundice
- 2. hepatomegaly and right upper quadrant pain
- 3. ascites and/or unexplained weight gain

2) Baltimore criteria

- Hyperbilirubinemia >2 mg/dL (34.2 µmol/L) before day 21 after transplant and, at least, two of the following features:
- 1. hepatomegaly (usually painful)
- 2. ascites
- 3. weight gain greater than 5% from baseline

3) Modified Seattle criteria

Occurrence of two of the following events within 20 days of transplantation:

- 1. hyperbilirubinemia (total serum bilirubin > 2 mg/dL)
- 2. hepatomegaly or right upper quadrant pain of liver origin
- 3. unexplained weight gain (> 2% of baseline body weight) because of fluid accumulation.

F. Baron Haematologica 1997; 82:718-725

Hepatic veno-occlusive disease

- Pathophysiology: complex
  - ➡ Damage to the hepatic venular and sinusoidal endothelial cells (ECs)
  - ➡ ECs detach and embolise downstream, obstructing sinusoidal blood flow
  - ➡ Hypercoagulate state
  - ➡ Reduction of glutathione enzymatic system activity ➡ Toxic metabolites ➡ Damage to hepatocytes and ECs

- Risk factors
  - Transplant related: mismatched, unrelated, PBMCs
  - Hepatotoxic drugs (Busulfan TBI (BCNU),methtrexate, progesterone)
  - Patient related: age, sexe, status of the liver, underlying disease, disease status, Karnofsky score

Classification of VOD according to its severity: Frequency and Outcome.

Mild VOD (8-23%) (mortality rate 2%)

- 1. no adverse effect from liver disease
- 2. no treatment for VOD
- 3. illness is self limited

Moderate VOD (48-64%)(mortality rate 14%)

- 1. adverse effect from liver disease
- 2. require treatment for VOD (such as diuretics)
- 3. medication to relieve pain from hepatomegaly)
- 4. complete resolution on day 100 with treatment

Severe VOD (23-28%)(mortality rate 50%)

- 1. VOD does not resolve before day 100
- 2. death from VOD
- 3. Dysfunction Multiorganic (Renal, respiratory, SNC) (mortality 80%)

Modified from McDonald GB et al. Ann Intern Med 1993; 118:255-67.

VOD – first line therapy

Symptomatic

- Restriction salt and water
- Maintain intravascular volume and renal perfusion (albumin, plasma expanders, transfusions –Hct >30%-)
- diuretics

Specific

- defibrotide

Summary of clinical response and overall survival with defibrotide for the treatment of severe hepatic veno-occlusive disease.

	Clinical response (%)	100-day mortality (%)
Phase II* (N = 149)	46#	42
Phase III$ (N = 102)	24	62
Meta-analysis‡ (N = 133)	29	60
IND protocol § (N = 104)	35	61

*[Richardson et al. 2010b].
$[Richardson et al. 2009].
‡[Richardson et al. 2010c].
§[Richardson et al. 2010a].
N = 141

PG Richardson : Ther Adv Hematol. Aug 2012; 3(4): 253–265

LUNG

Diffuse Alveolar Haemorrhage

- Similar to VOD but affecting the lung.
- Incidence is 3-7%
- Within 30 days post transplant
- Risk factors, not related to low platelets count. Older age, previous thoracic radiation, myeloablative conditionning and aGVHD.
- Treatment: steroids? rFVIIa?
- 75% mortality.

Idiopathic pneumonia syndrome (IPS)

- Lung injuries: toxic, inflammatory, immunologic and infectious.
- Incidence 8-10% (2-3% in RIC)
- Around Day 21
- Fever, non productive cough, hypoxemia, diffuse alveolar or interstitial infiltrates , exclusion of infection.
- Risk factors: myeloablative conditionning, age > 40years, aGVHD, TBI,
- Steroids? antiTNFa?
- Mortality 50-70% (97% if mechanical ventilation required)

KIDNEY

Changes in renal function in long-term survivors of allo-HSCT

eGFR recorded 3 months after HSCT was significantly decreased compared with the eGFR recorded before HSCT.

- Acute kidney injury (AKI) during HSCT,
  eGFR decreased significantly at 3 months after HSCT.
  After 3 months, the eGFR recovered to reach a lower level than in patients without AKI.

- Low eGFR before HSCT (< 90 ml/min)
  Decreased significantly at 3 months after HSCT,
  maintained during the 60 months after HSCT.

- Hypertension (HTN)
  eGFR decreased significantly at 3 months after HSCT.
  the eGFR decreased consistently and slowly from 3 to 60 months.

Kang SH : Clin Nephrol 2012 Mar;77(3):225-30.

Table 4 Risk factors for acute renal injury by multivariate analysis adjusting for demographic and baseline characteristics

Variable	Acute renal injury			
	B	HR	95% CI	*P*
Disease status	1.182	2.945	1.293–6.421	0.030
HLA	0.521	1.684	0.648–4.378	0.285
Conditioning regimen	1.147	2.463	1.757–4.320	0.034
aGVHD	1.268	3.553	1.809–6.978	0.003
Sepsis	1.249	3.215	1.189–6.333	0.023
VOD	1.199	3.487	1.392–6.524	0.008

Abbreviations: HR, hazard ratio; CI, confidence interval; HLA, human leukocyte antigen; aGVHD, acute graft-versus-host disease; VOD, hepatic veno-occlusive disease.

ZhengPing Yu: Chinese journal of cancer 2010

Thrombotic Microangiopathy (TMA)

- Endothelial dysfunction with intravascular platelet activation and thrombi formation
- ADAMTS13 activity very rarely < 10%
- Incidence 7-15%
- Around day 60 (4d -2years)
- Risk factors: TBI, Calcineurin inhibitors, sirolimus, unrelated or mismatched donor, GVHD, CMV infection.
- Treatment?: treat underluying causes (stop calcineurin inhibitors ?, treat infections, and GVHD) Rituximab? Daclizumab? Defibrotide?

Diagnostic criteria for HSCT associated TMA

- Bl & Mar Transplant Clin Trials Network consensus
  1) >2 schistocytes
  2) Increased LDH
  3) Renal (X2 ser creat) and/or neurologic dysfunction
  4) Negative direct and indirect coombs

- International Working Group
  1) >4 schistocytes
  2) de novo, prolonged or progressive thrombopenia
  3) Increased LDH
  4) Decrease in Hb
  5) Decrease in serum haptoglobin.

Clinical Forms

- 1) CNI-associated

  Nephrotoxicity or neurotoxicity with microangiopathic haemolytic anaemia

  Reversible after stopping CNI.

- 2) Not associated with CNI

a- Conditionning associated HUS,

  primarly affecting kidney (renal failure, hypertension, hemolytic anemia and thrombopenia)

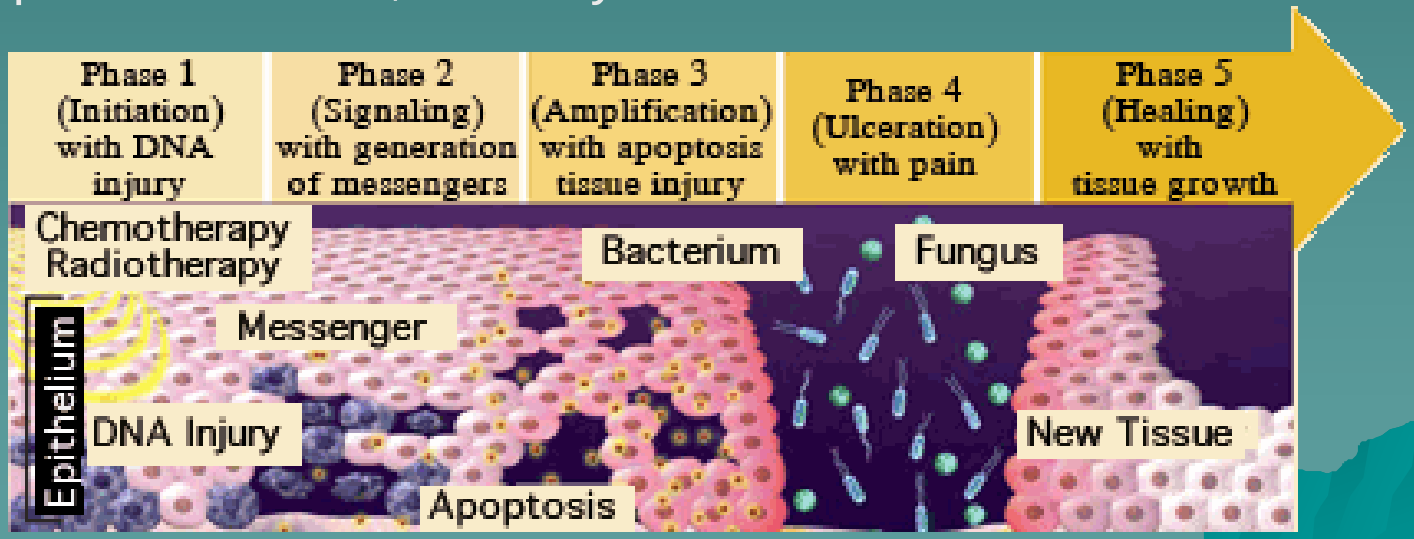
b- Fulminating multifactorial TMA.

  Early after HSCT, renal failure, CNS disturbance, hypertension, hemolytic anemia, thrombocytopenia, associated with aGVHD, viral or fungal infection.

ORAL and GI MUCOSA

MUCOSITIS

- Characterized by damage to the epithelium of the oropharyngeal cavity and GI tract (CT-RT, MTX, Xerostomia, Infections, aGVHD)
- Rapidly dividing basal cells of the oral mucosa are among the body cells vulnerable to damage
- 75% of all patients undergoing BMT
- Inadequate oral intake, electrolytic imbalance



Phases of Mucositis

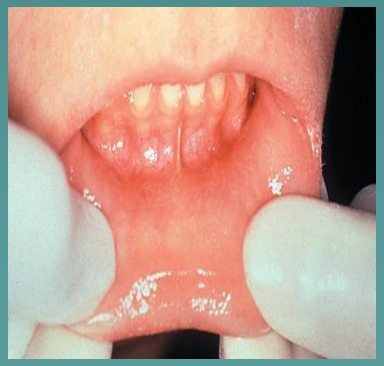
Adapted from Sonis. Nat Rev Cancer. 2004;4:277-284.

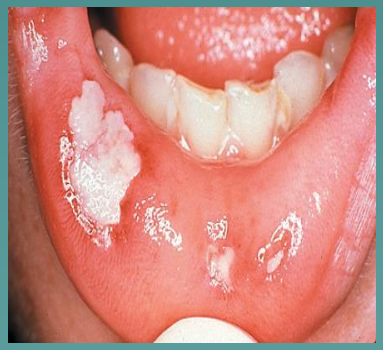
WHO's Oral Toxicity Scale

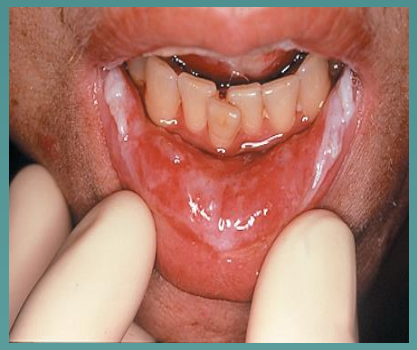
World Health Organization's Oral Toxicity Scale

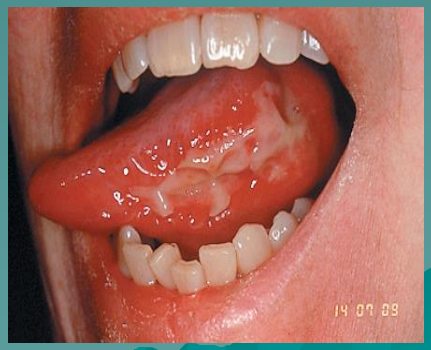
Grade 1	Grade 2	Grade 3	Grade 4
Soreness ± erythema	Erythema, ulcers; patient can swallow solid food	Ulcers with extensive erythema; patient cannot swallow food	Mucositis to the extent that alimentation is not possible

Severe Mucositis









Patrick J. Stiff, MD
Loyola University Medical Center

Differential Diagnosis: Oral

Disease/Injury	Causality	Clinical Presentation/Lab Findings	Severity	Treatment Options
Oral mucositis	**Chemotherapy and radiation therapy (Cyclophosphamide,TBI, Busulfan, Fludarabine)**	**Diffuse redness, ulcerations, and pain, particularly in areas where teeth abut tissue**	**Varies; in BMT setting up to 98% have Grade 3/4**	**Palliative rinses, narcotics, palifermin in the BMT setting**
Aphthous stomatitis	Etiology not identified	Single painful ulcer	Localized, but painful; maximum grade 2	Topical
Herpetic mucositis	HSV1	Usually several spots; ulcerative	Usually grade 1-2	Acyclovir, valacyclovir, foscarnet
Oral thrush	Candida	Varies from painless to mild soreness; whitish plaques	Usually grade 0-1	Nystatin rinses; fluconazole and other azoles
Denture/oral trauma	Dentures	Common in elderly patients with loose-fitting dentures	Can limit calories	Repair, removal of dentures
Gangrenous stomatitis	Bacterial infections	Necrotic pseudomembranes	Rare, can be severe	Antibacterials that treat oral aerobes and anaerobes
Acute necrotizing stomatitis	Bacterial infections in immune deficient patients	Pain, fever, necrotic, bloody ulcers	Grade 3/4	Control of infection

Differential Diagnosis: GI

Disease/ Injury	Causality	Clinical Presentation/ Lab Findings	Severity	Treatment Options
Mucositis of the GI tract	Chemotherapy and radiation (Cyclophosphamide, TBI, Busulfan, Fludarabine)	Typhilitis, diarrhea, ileus, bowel obstruction, pain, discomfort.	Mild to life-threatening	Supportive care, treatment of infectious complications
Crohn's disease/ Ulcerative colitis	Autoimmune	Diarrhea, pain, bowel obstruction hematochezia	Mild to life-threatening	Steroids, antibody therapy with agents such as infliximab anti-inflammatory agents
Acute GVHD	Alloimmune	Diarrhea, pain hematochezia, ileus	Mild to life-threatening	Steroids, ATG, antibody therapy with agents such as infliximab
C difficle colitis	C difficle toxin	Diarrhea	Mild to life-threatening	Antibacterials: metronidazole, vancomycin
Viral colitis, e.g., CMV	Specific viral infection	Diarrhea	Mild to life-threatening	Antivirals: ganciclovir, foscarnet

Haemorrhagic Cystitis (HC)

- Cyclophosphamide – Busulfan – TBI (rare) – Fludarabine (rare)

  Direct toxicity on the urothelium

  Several days after chemotherapy

  1-25% depending of preventing mesure (Hyperhydration-Mesna)

- Viral HC (polyomavirus) appears later >30 days (5-25%)

Conditionning regimen Toxicity

Cyclophosphamide:

- **Cardiovascular : A**cute cardiac toxicity, systolic dysfunction. Congestive heart failure after high dose (rare).
- **Endocrine:** Syndrome of inappropriate antidiuretic hormone (SIADH) high doses (>than 50 mg/kg).

Busulfan:

- Pulmonary fibrosis
- Hyperpigmentation

Fludarabine:

- Central and peripheral nervous system: weakness/fatigue (asthenia) (up to 31%), headache (up to 9%), hearing disturbances (6%), paresthesias (4%), confusion (1%), visual disturbances (3%).
- Pulmonary toxicity : Adult respiratory distress syndrome,, pulmonary hemorrhage, pulmonary fibrosis. Cough (10% to 44%), dyspnea (1% to 22%).
- Patients with creatinine clearance 30 to 79 mL/min should have their Fludarabine dose reduced and be monitored closely for excessive toxicity.

Immunosuppressors : Side Effects

- Cyclosporin/Tacrolimus: Nephrotoxicity, microangiopathy, neurotoxicity, diabetes, hyperkalemia, metabolic acidosis, hypertension, hyperlipidemia, gingival hyperplasia, hypertrichosis.

- MMF: Myelosuppression, gastrointestinal effect, kidney tubular necrosis, edema

- Sirolimus: Hyperlipidemia, myelosuppression, skin rash, interstitiel pneumonitis, pleural effusion, alveolar proteinosis edema, increased creatinine, proteinuria, microangiopathy, hypertension, chest pain, gastrointestinal effect, hepatotoxicity, headache, tremor, insomnia,

- Corticosteroids: Diabetes, Hypertension, Obesity, Osteoporosis Avascular bone necrosis, growth retardation, cushingoid syndrome, psychosis, poor wound healing, adrenal suppression, cataract.

Xupeng CE Biol Blood Marrow transplant 2008 May: 14(5) 518-530

Infections related to Myeloablation and Immunosuppression

- **Aplastic phase until neutrophil recovery**
  risk increased -- mucosal damage -- TBI
  Bacterial sepsis (febrile neutropenia 30% documented)
  Fungal infection (aspergilose up to 20%,)
  Viral infection (HSV)

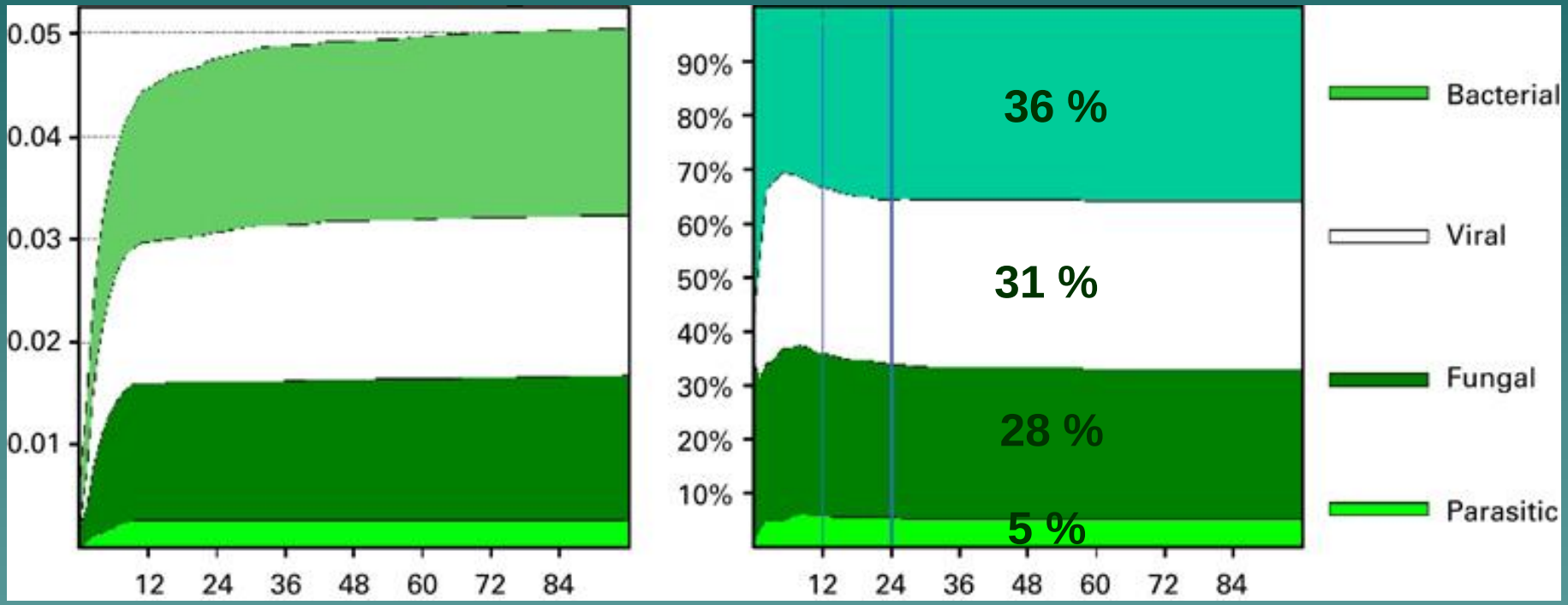
- **Engraftment until cell-mediated immune response recovery CD4+ T cells >200/microliter**
  Viral infection (CMV, adenovirus, RSV, EBV, HHV6, polyomavirus)
  Fungal infection (>risk if steroids for GVHD, >20%, 50% mortality)
  Toxoplasmosis (PCR 16% - disease 6%, no Bactrim and GVHD)
  Pneumocystisis.

- **Late phase**
  IgG2 deficiency, decreased response to polysaccharide antigens
  (S pneumoniae, H Influenzae)

Factors affecting Immune Reconstitution

- Host factors: Age, sex, conditionning regimen (ATG), initial pathology
- Genetic differences: HLA, mAgs, SNPs on genes linked to microbial responses.
- Source of HSC: Marrow, PBSC, CB, TCD,
- Post HSCT events: immunossupressive treatments, aGVHD, cGVHD

Cause of death after allo-HSCT in leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time



Stacked cumulative incidences (left panel) and relative contribution (right panel) of bacterial, viral, fungal or parasitic infections to infectious death over follow-up time. All four cohorts combined. Time in months post HSCT.

A Gratwohl, Bone Marrow Transplantation (2005)

Late Effects

Mortality →

Morbidity →

Late Effects I

- **Eye:** Cataracts: TBI (80%) - Steroids
  Keratoconjonctivitis sicca syndrome: TBI (10%) - cGVHD (40%)
  Retinopathy: ischaemic (10%): TBI - cyclosporin- Infectious

- **Heart:** Restrictive or dilated cardiomyopathy, Arythmia,
  Autonomic neuropathy: TBI - Anthracyclin

- **Respiratory:** Chronic obstructive lung disease (20%),
  Bronchiolitis obliterans (2-14% -mortality 50%):
  Infections, GVHD, Smoking
  Restrictive lung disease: TBI - Chemo- Infection

- **Liver:** liver cirrhosis : Iron overload, cGVHD

- **Kidney:** nephropathy, hypertension : TBI Chemo Cyclosporin

- **Skeletal:** Avascular necrosis (4-10%) (hips 80%): steroids - TBI
  Osteoporis (50%): steroids, cyclosporin, tacrolimus
  hypogonadism, TBI, chemo, Immobility

Late Effects II

- **Oral:** chronic stomatitis, dental effects: cGVHD - TBI
- **Thyroid gland** (7-15%): hypothyroidism: TBI
- **Gonadal function**: gonadal failure, male usually compensate, female SHRT needed : TBI - Chemo (Busulfan),
- **Fertility:** infertility: TBI - Chemo
- **Nervous system:** Leukoencephalopathy: Cranial radiation, IT, Chemo
  Peripheral neuropathy: Chemo GVHD
- **Vascular:** Atherosclerosis, cardio and cerebrovascular events: TBI, GVHD,
- **Malignant complication:** B cell-PTLD (1%): EBV and TCD
  Solid tumours 8% at 20y (X8): TBI - cGVHD

Psychological aspects of HSCT

- **Psychological morbidity: Anxiety, depression**
  - The treatment that may cure may kill
  - Search for suitable donor
  - Long hospitalisation, side effects
  - Anxiety during follow up: infection, GVHD
  - Fear of relapse

- **Quality of live**
  - Low energy level
  - Fear of loosing job
  - Infertility
  - Sexual problems (30% men, 80% women)
  - Poor physical, psychological and social functionning
  - Family distress