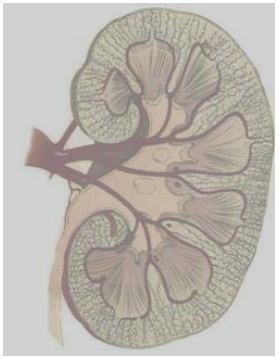
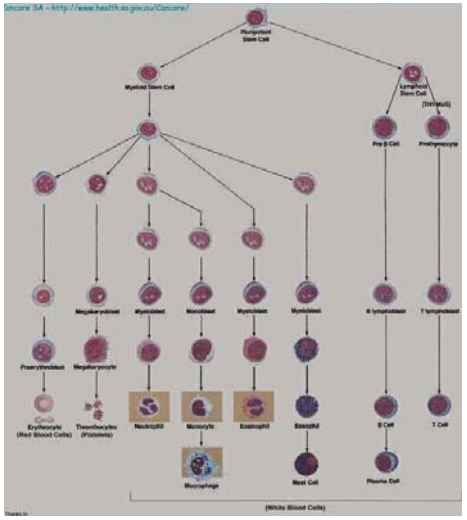
Complications pulmonaires de la Transplantation de moelle point de vue de l'hématologue

Hôpitaux Universitaires de Genève
Service d'Hématologie

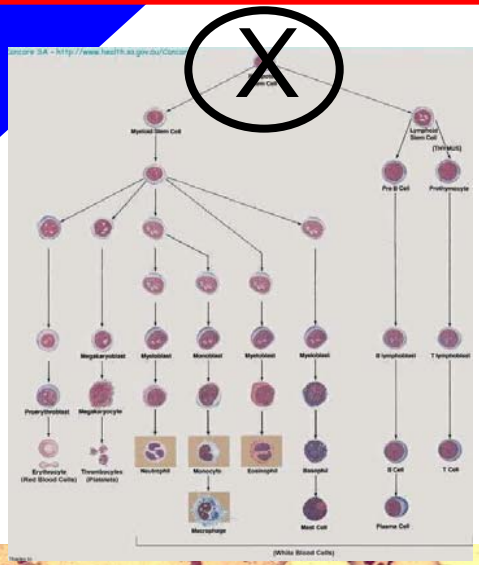
Pr Jakob R Passweg MD MS

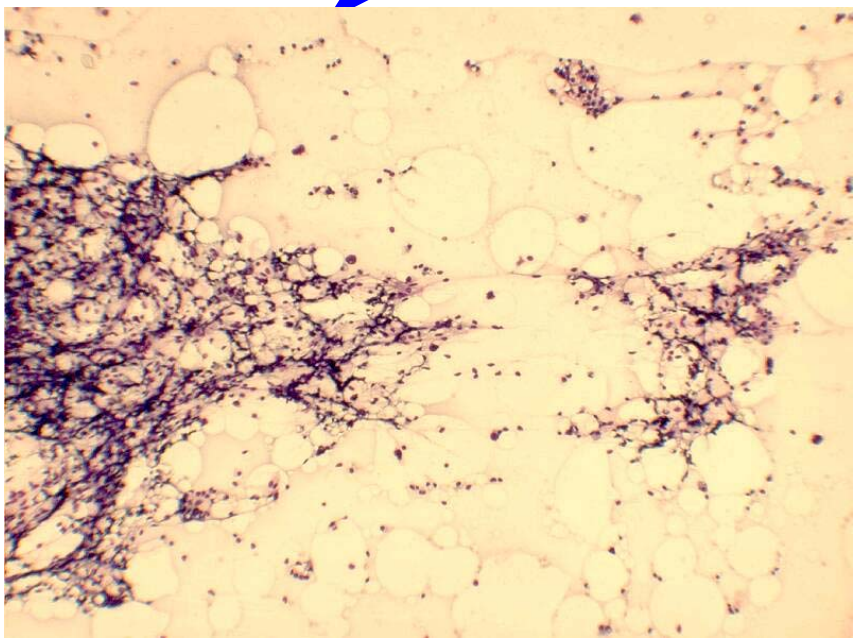
Two vectors of rejection in HSCT

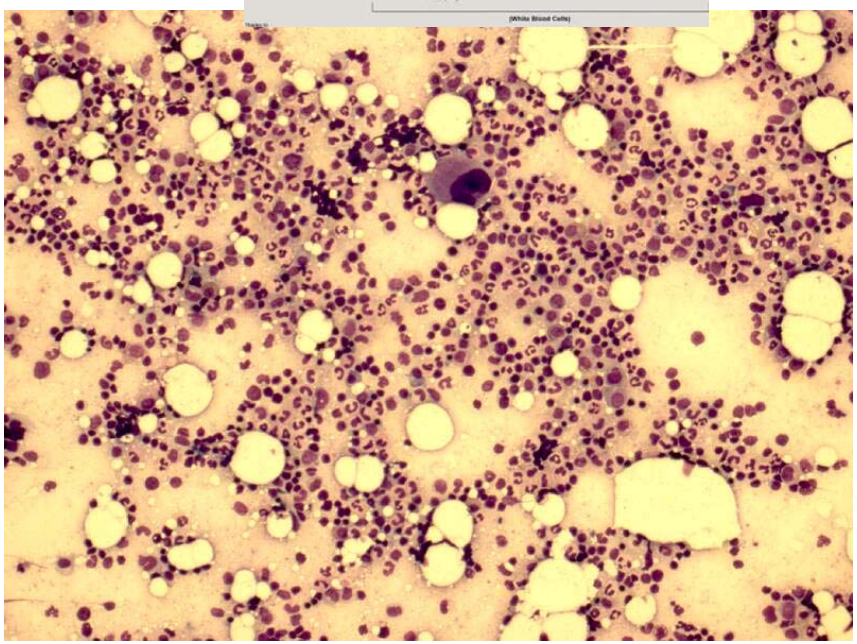




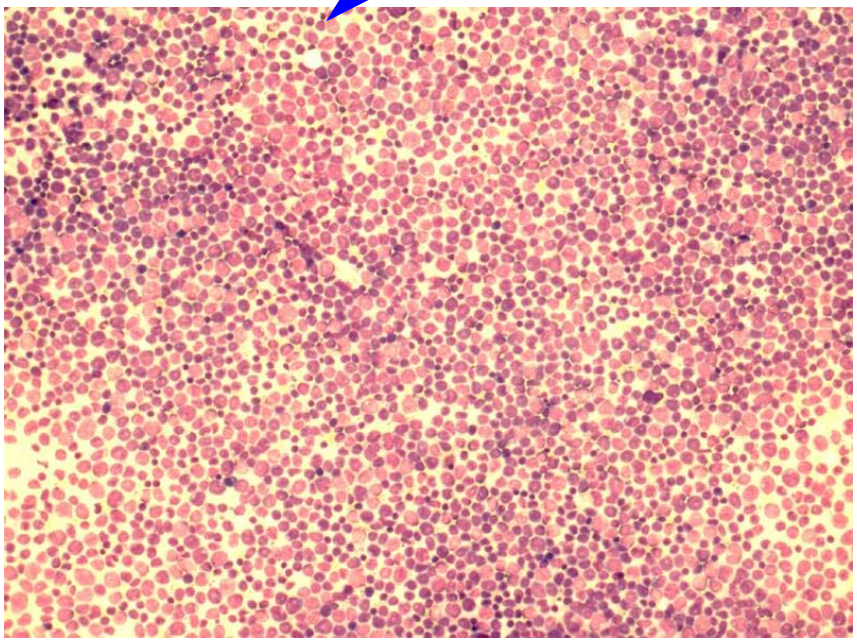
Aplasie médullaire

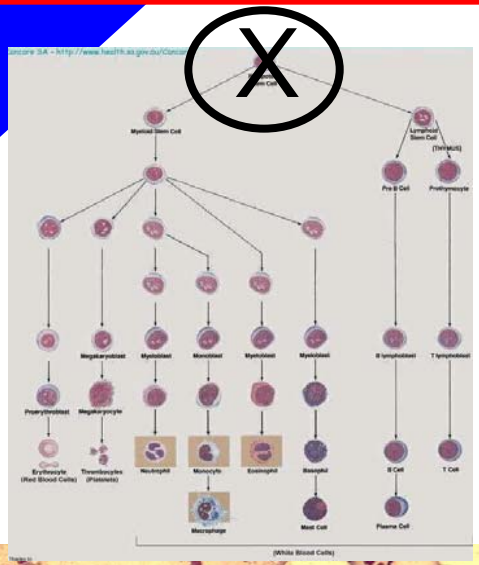


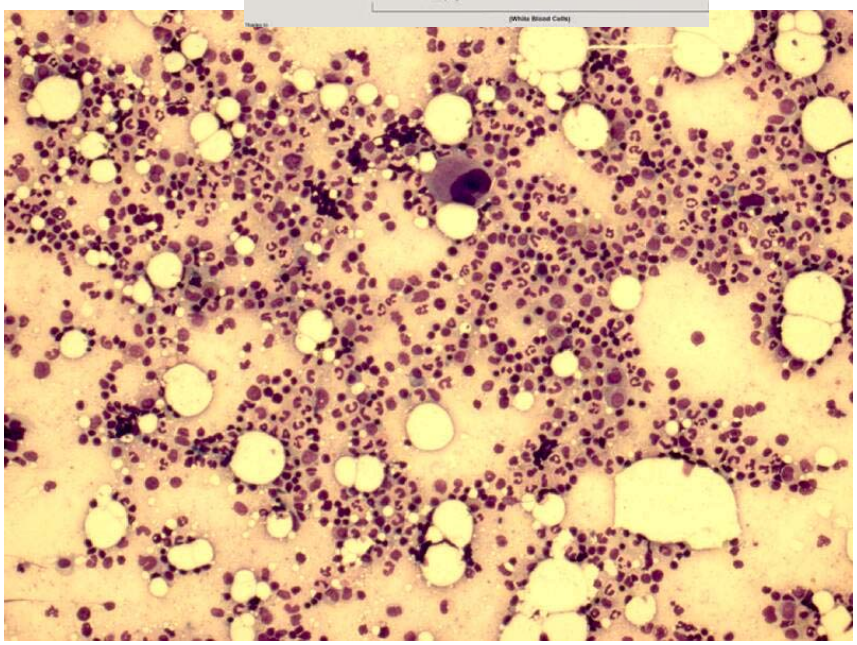




leucémie




Myeloid Stem Cell
Lymphoid Stem Cell
Pro B Cell
Prothymocyte
Megakaryoblast
Myeloblast
Monoblast
Myeloblast
Myeloblast
B lymphoblast
T lymphoblast
Proerythroblast
Megakaryocyte
Erythrocyte (Red Blood Cells)
Thrombocytes (Platelets)
Neutrophil
Monocyte
Eosinophil
Basophil
B Cell
T Cell
Macrophage
Mast Cell
Plasma Cell
(White Blood Cells)



EBMT Activity survey on HSCT in 2008: main indications

Indication	Allogeneic 1st Tx.	Autologous 1st Tx.	Total
Leukaemias*	7538	973	8511
Lymphoproliferative disorders	1664	13220	14884
Bone marrow failures	608	2	610
Solid tumours	62	1409	1471
Non-malignant disorders	696	167	863
Others	75	26	101
Total	10643	15797	26440

* includes CLL

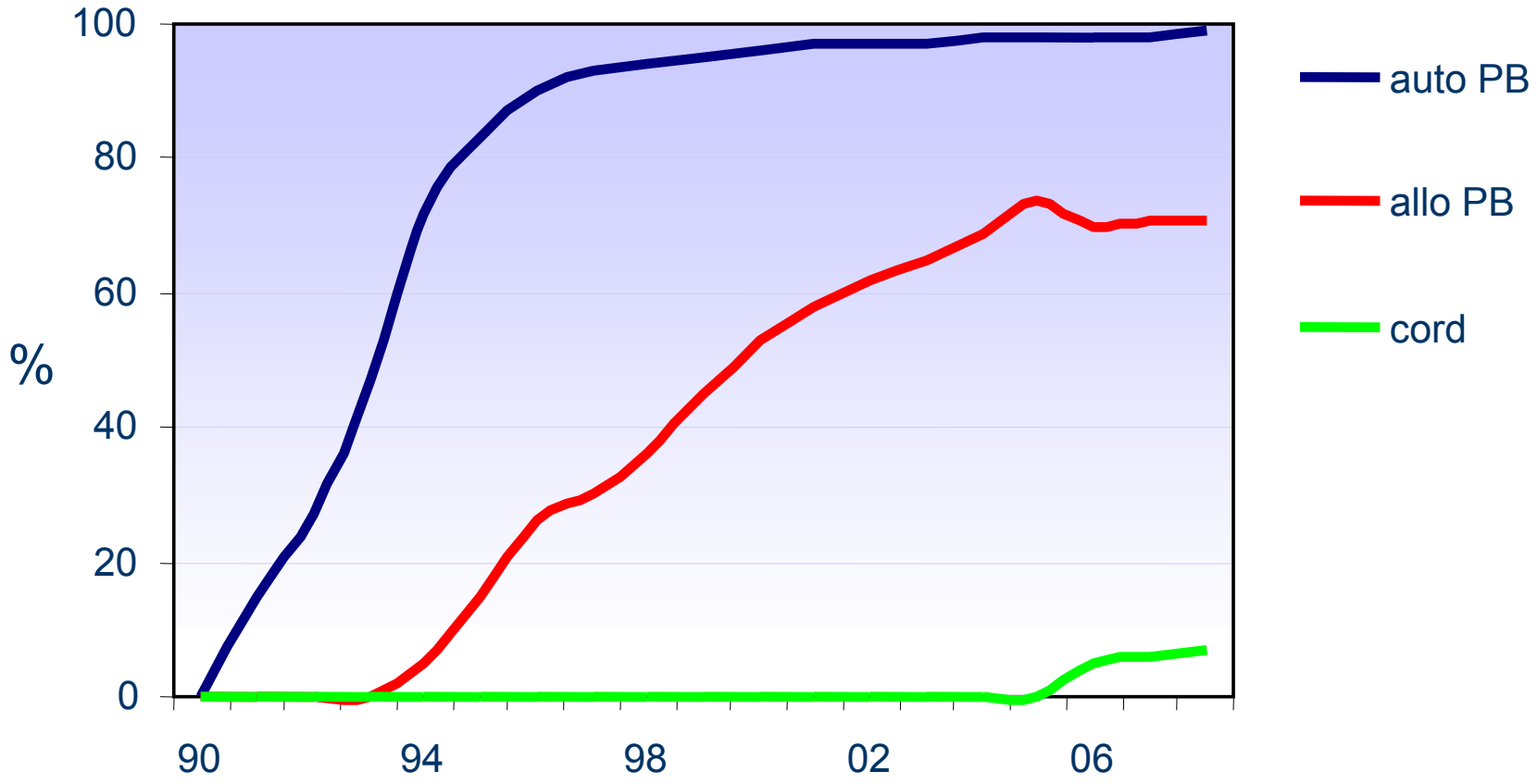
2008: preliminary data

EBMT Activity survey on HSCT in 2008: donor type and source

	Source			
Donor	BM	PBSC	Cord	Total
Allogeneic total	2422	7530	691	10643
HLA-id	1270	3544	46	4860
HLA-nid	117	398	2	517
Twin	13	29	0	42
Unrelated	1022	3559	643	5224
Autologous	199	15598	0	15797

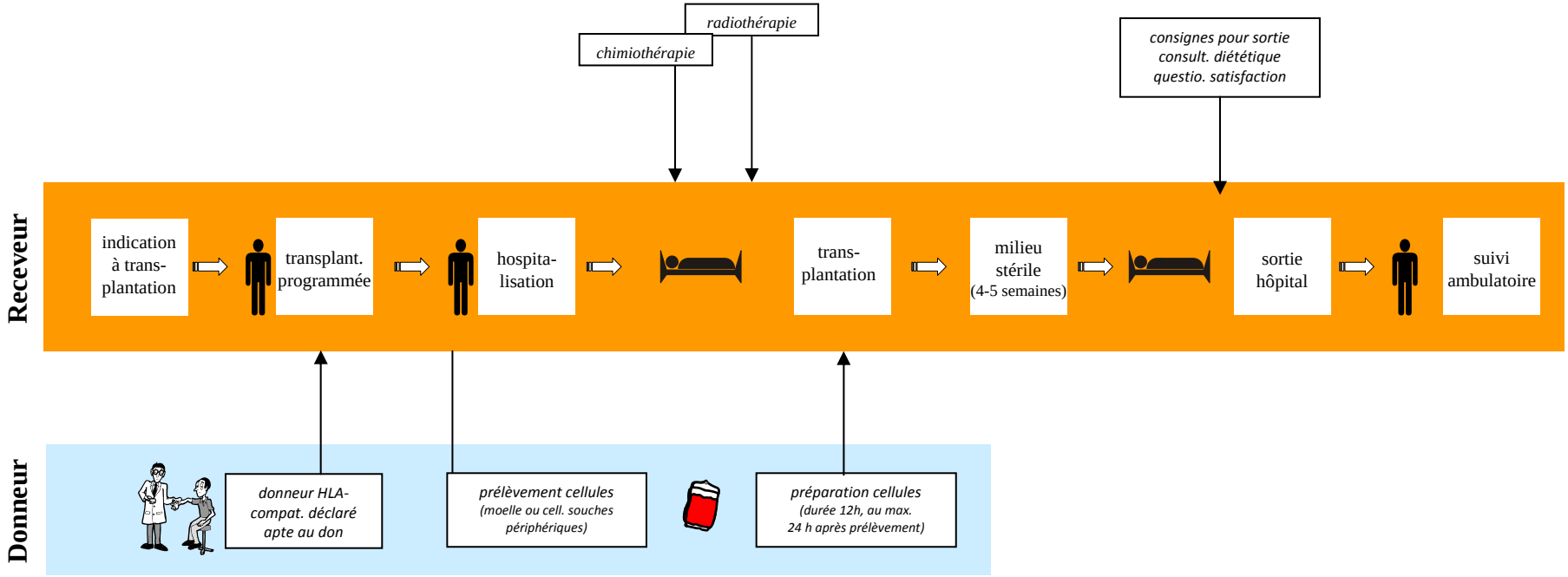
2008: preliminary data

EBMT Activity Survey on HSCT 1990-2008 changes in PBSC and Cord



2008: preliminary data

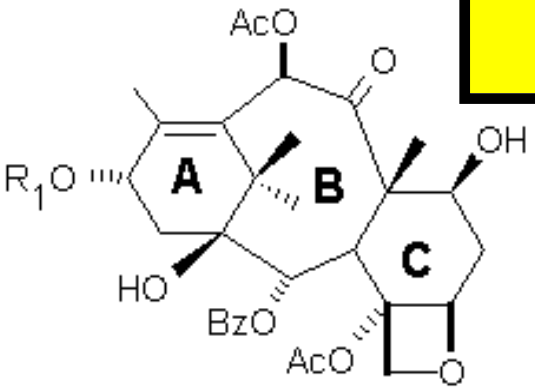
Déroulement d'une transplantation de cellules souches hématopoïétiques



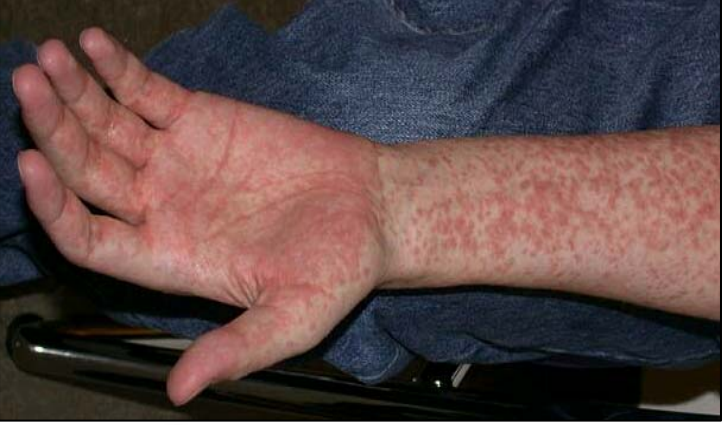
Donneur

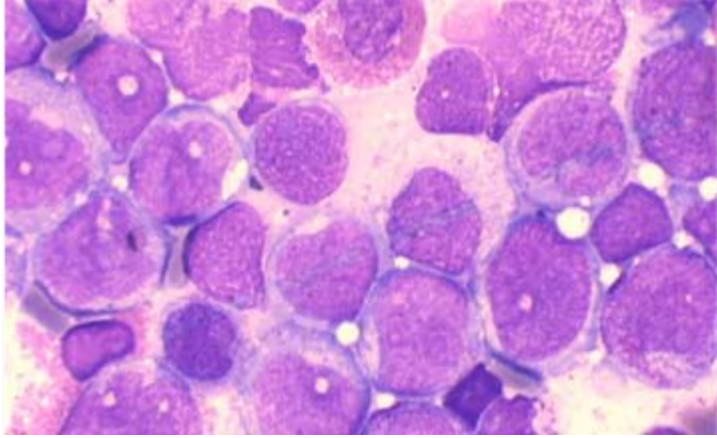
⓪ Jumeaux univittelins	2%
❶ Fratrie HLA-identique	25%
❷ Volontaire HLA-identique	50%
❸ Famille avec mismatch	90%
❸ CS du cordon ombilical avec mm	90%

Chimiothérapie & Irradiation
Effet antileucémique
immunosuppression

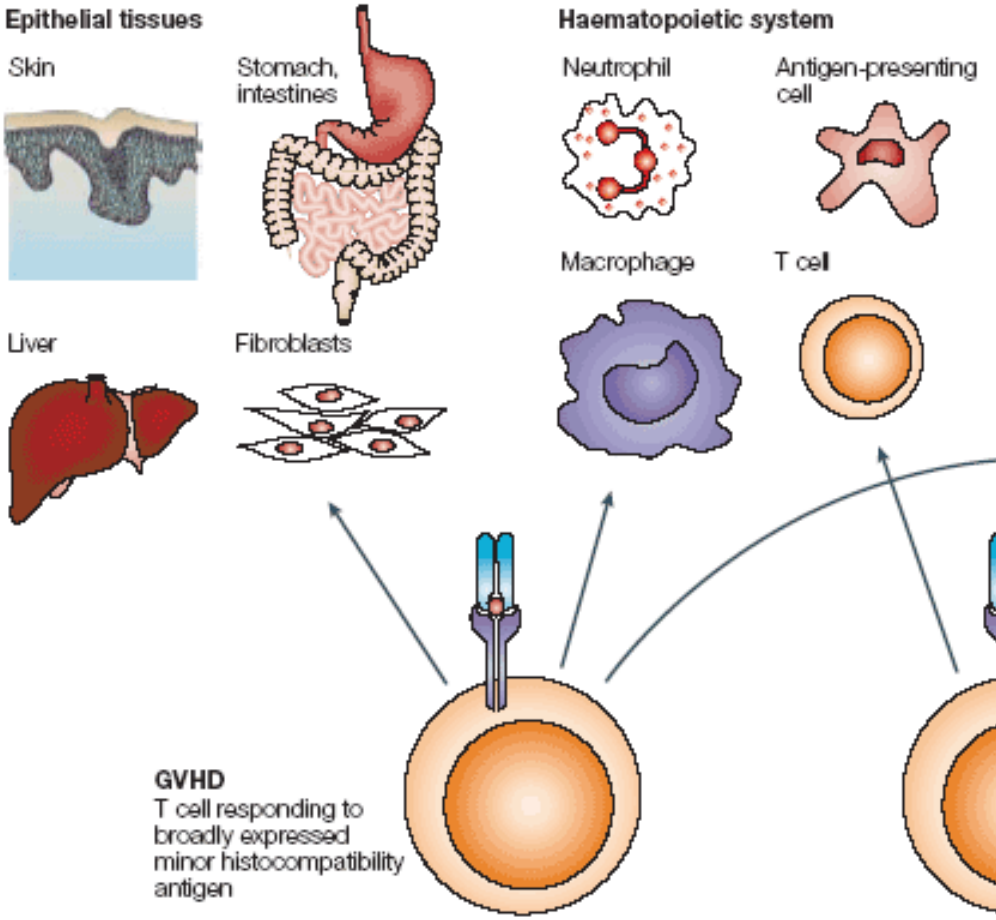


Radiation:
- kills leukemia
- immunosuppressive
- independent of blood supply
- no crossresistance with chemotherapy
- no sanctuary sites



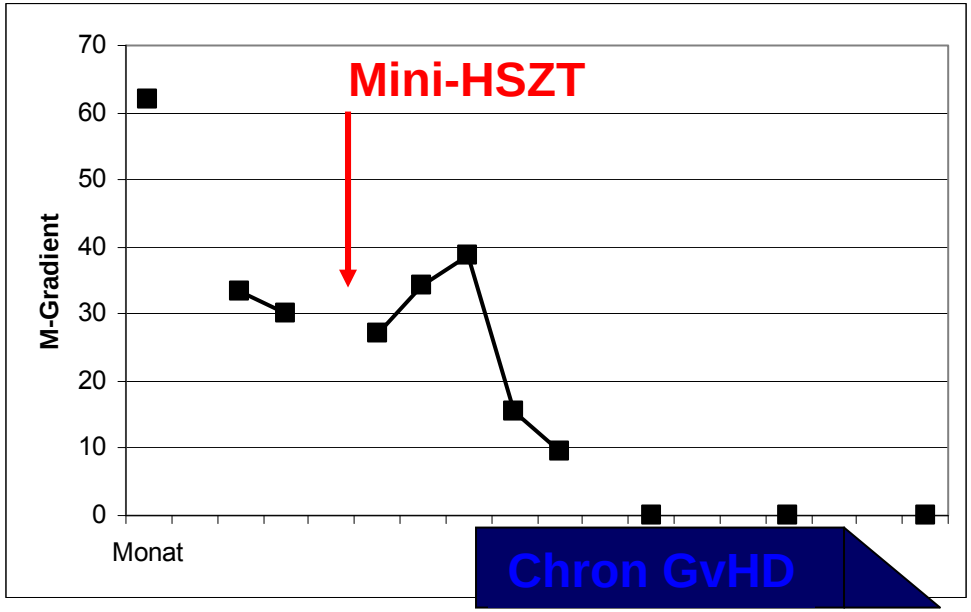


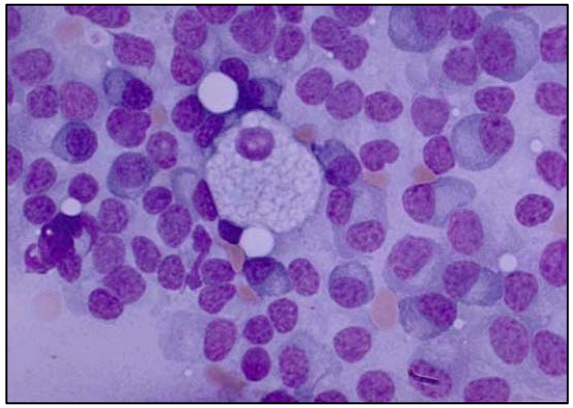
GVH

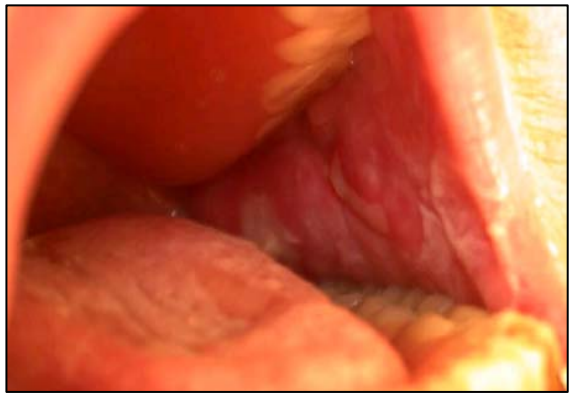

Epithelial tissues
Skin
Stomach, intestines
Liver
Fibroblasts
Haematopoietic system
Neutrophil
Antigen-presenting cell
Macrophage
T cell
GVHD
T cell responding to broadly expressed minor histocompatibility antigen
GVL
T cell responding to haematopoietic-restricted minor histocompatibility antigen

GVL

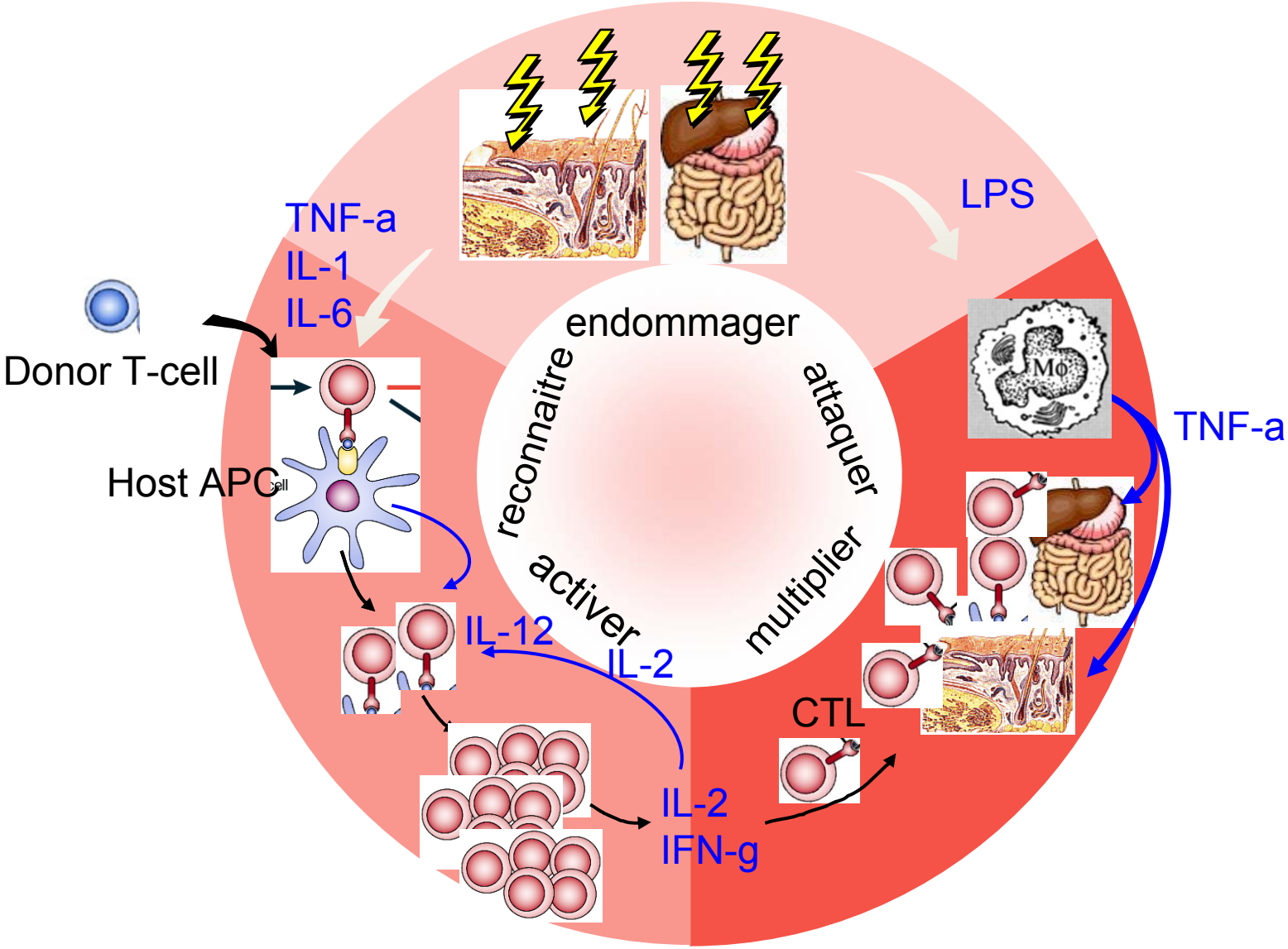
microtransplant: fludarabine / 2 Gy TBI



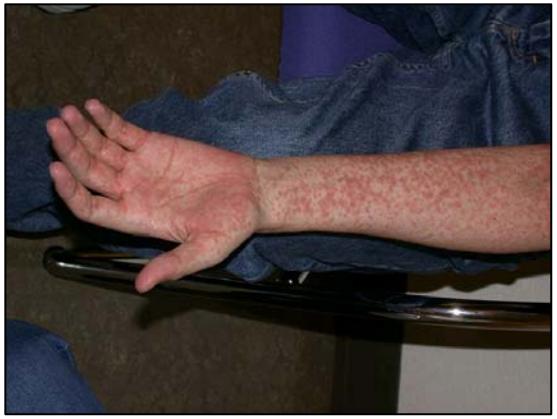


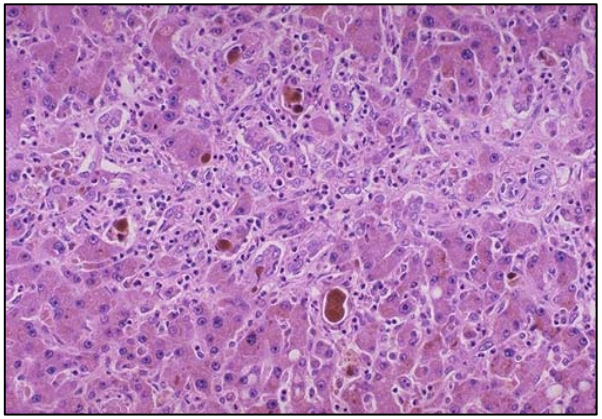


Immunology of aGvHD: the vicious circle

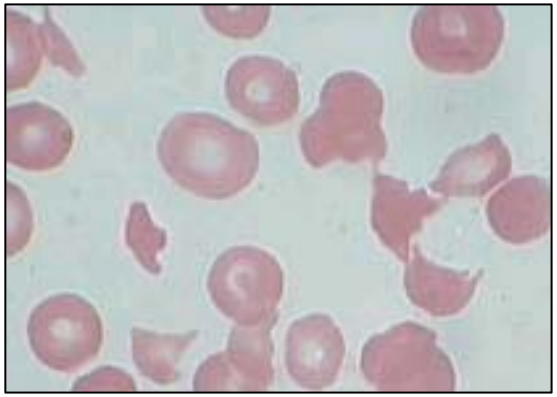


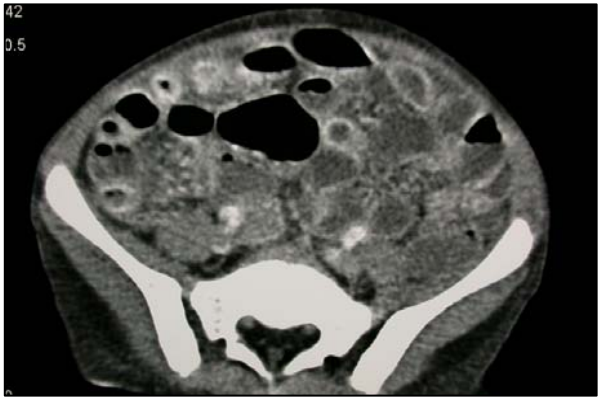
Acute GvHD j14-100



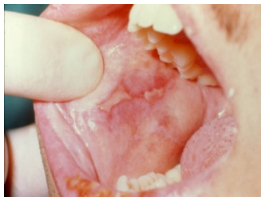


inflammation
- skin
- mucosal
- gut
- liver

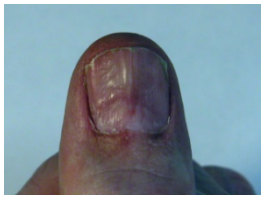




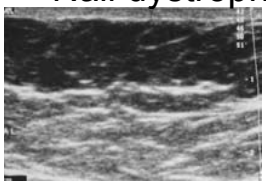
Dry eyes



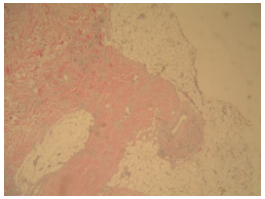
Oral lesions



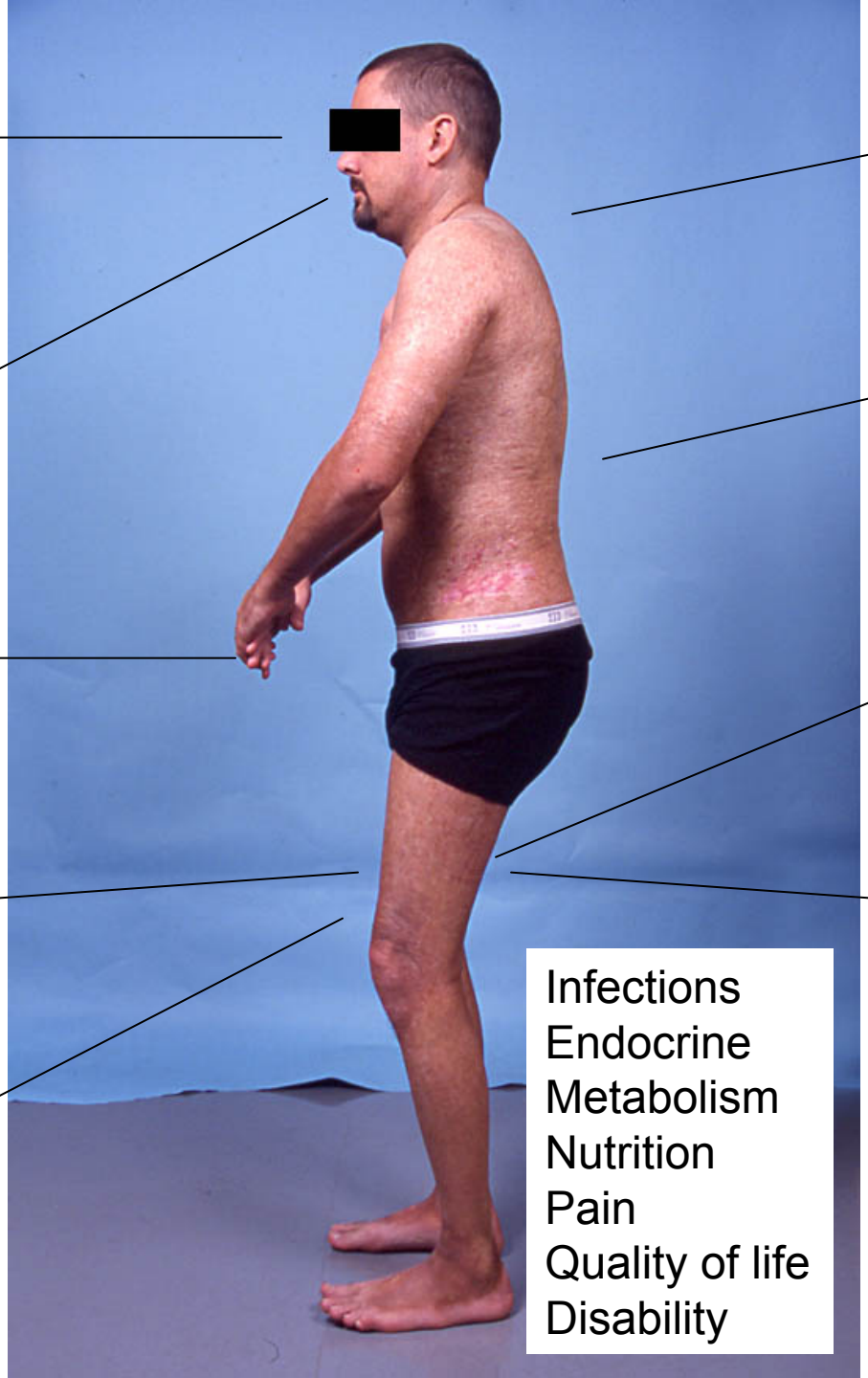
Nail dystrophy



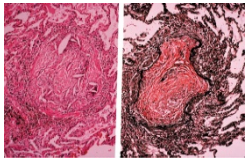
Skin sclerosis



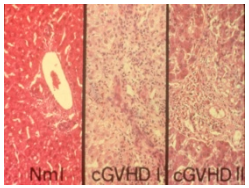
Deep sclerosis



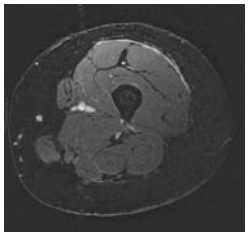
Infections
Endocrine
Metabolism
Nutrition
Pain
Quality of life
Disability



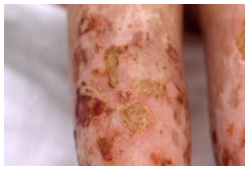
Bronchiolitis obliterans



Loss of bile ducts



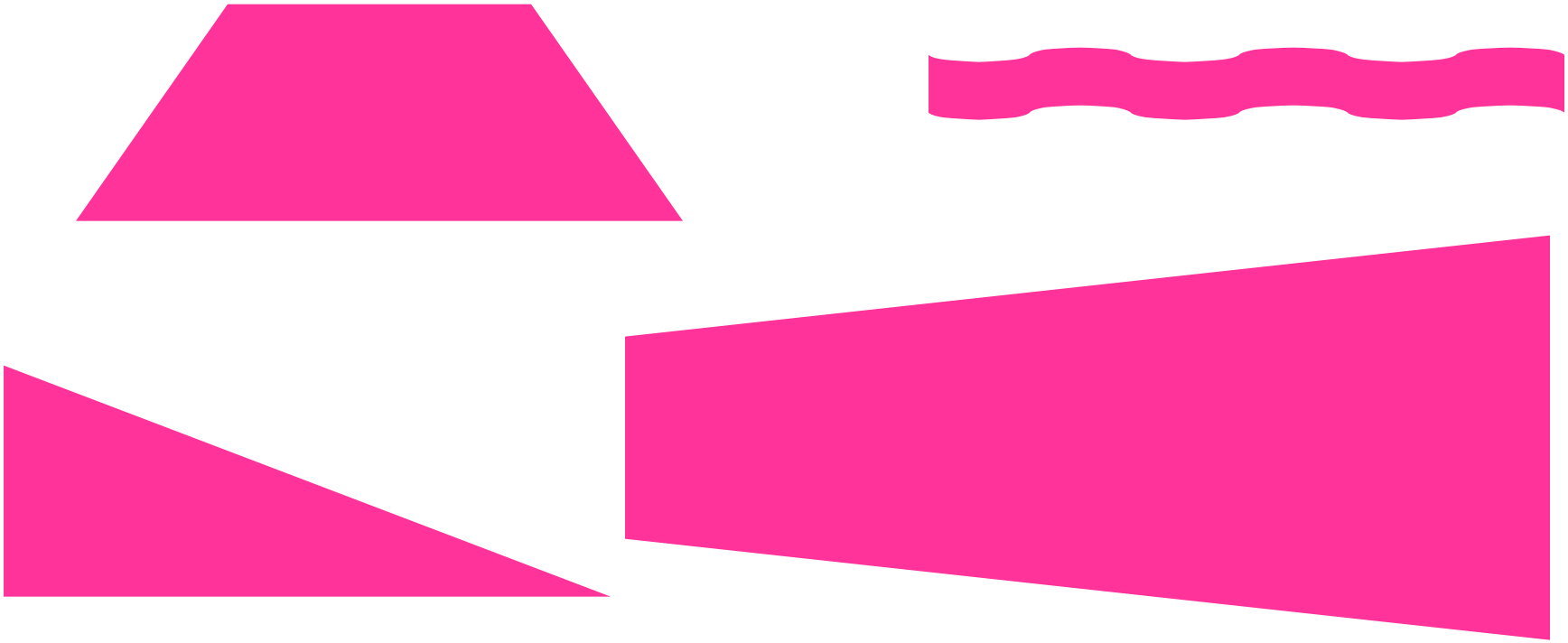
Fasciitis



Skin ulcers

Spectrum of manifestations In cGVHD

Clinical course of cGvHD

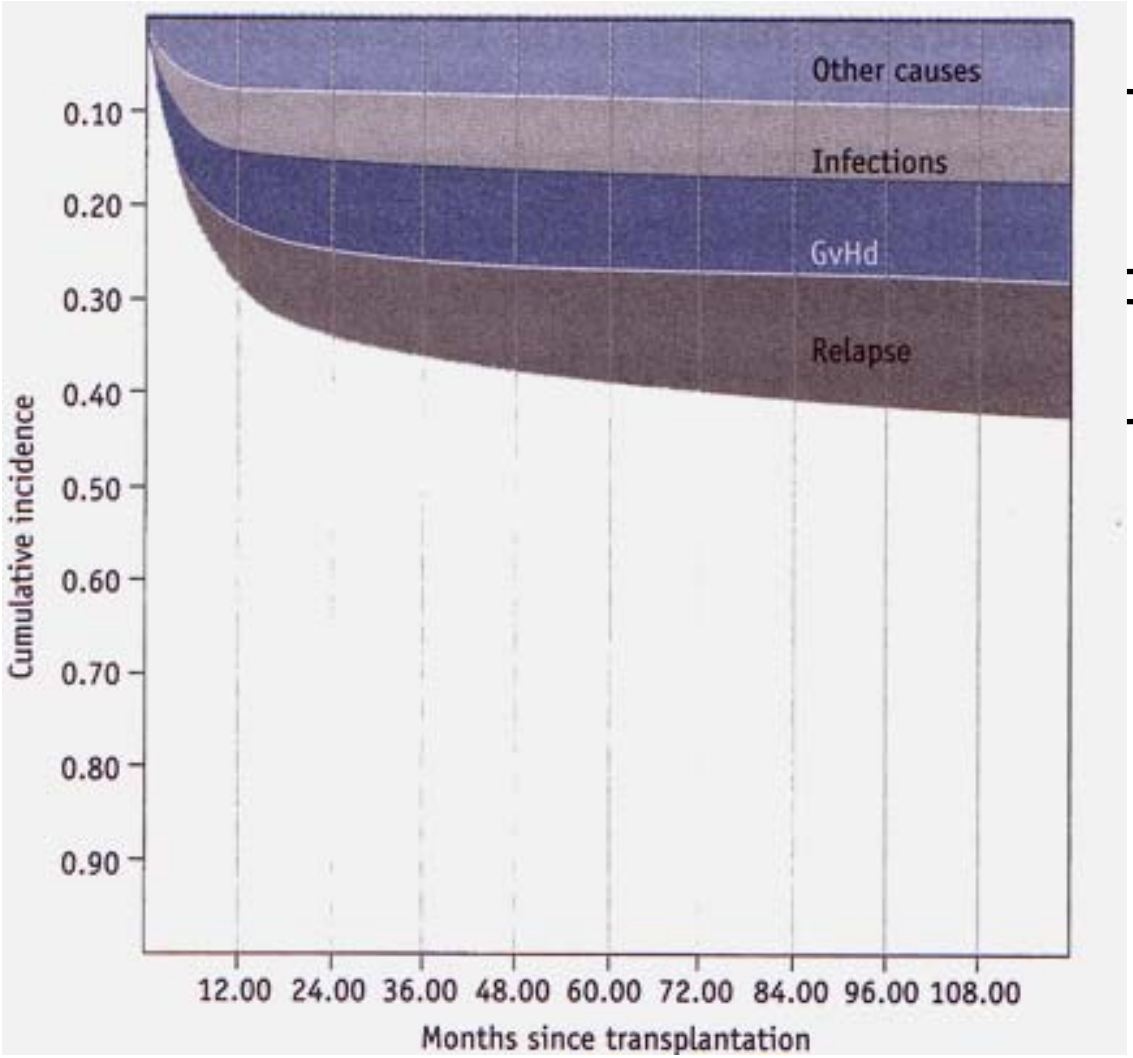


aGvHD: inflammatoire

cGvHD: fibrotique

Mortalität nach allogener HSZT:

Rezidiv (GvL ungenügend) ~ GvHD (Infektionen)



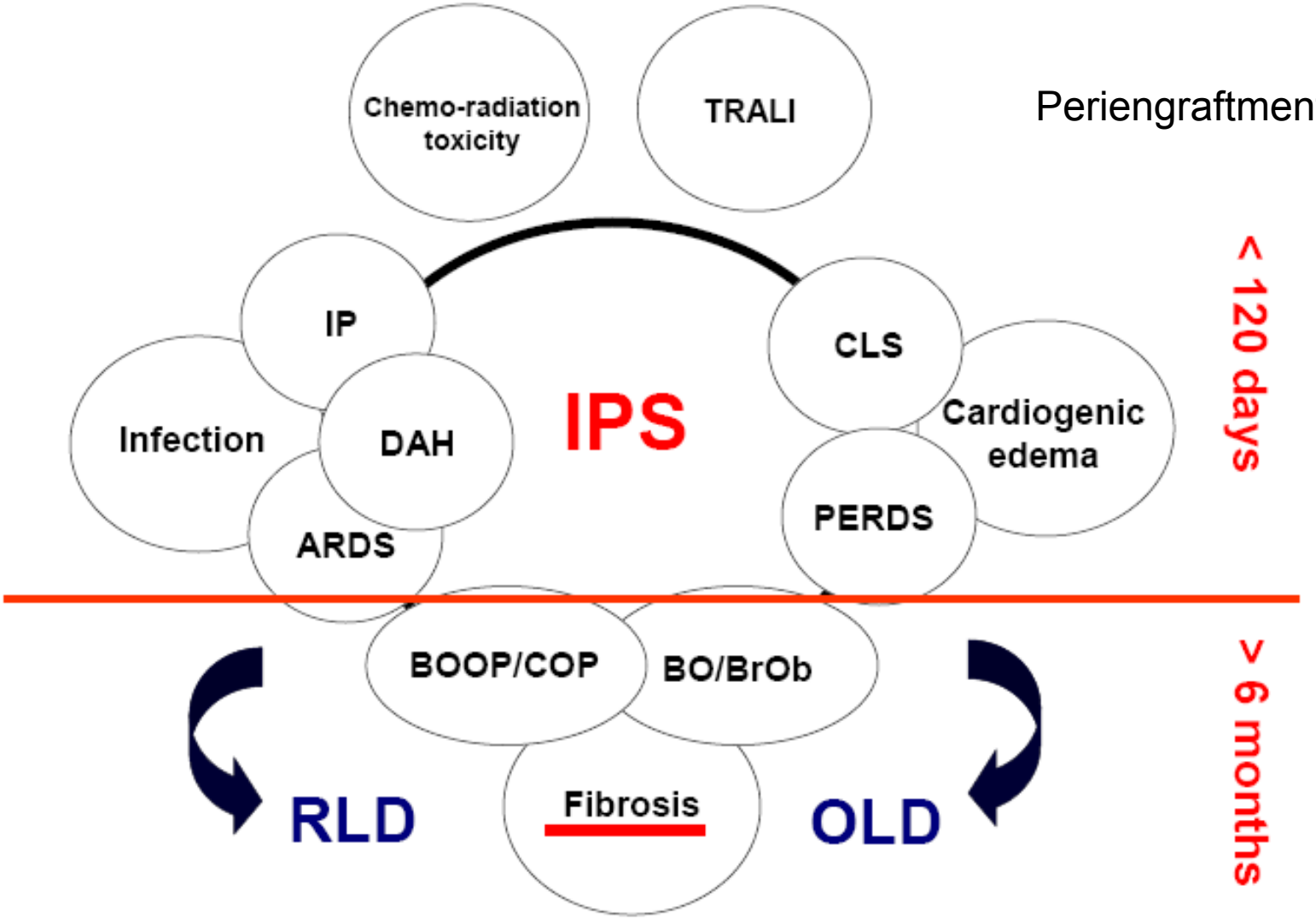
GvH

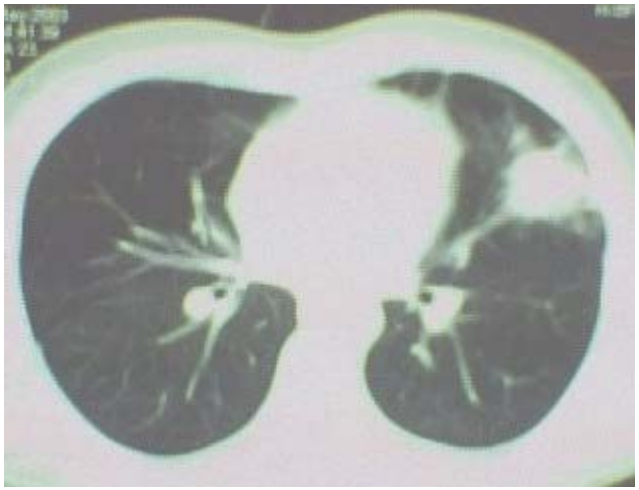
Ø GvL

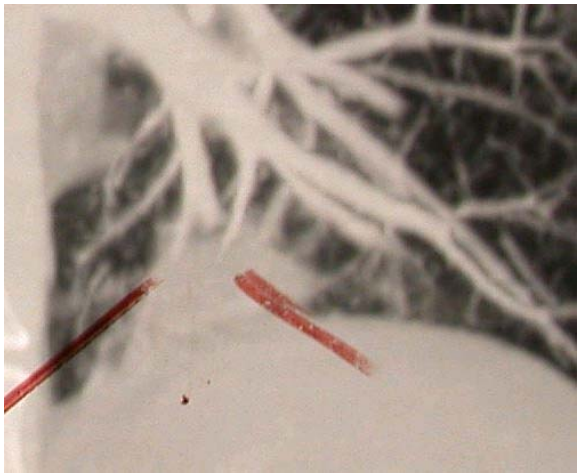
DD: atteinte pulmonaire

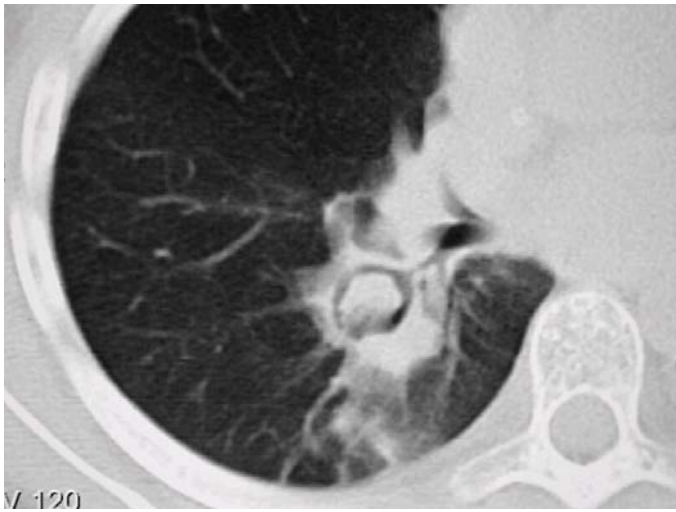
- Toxicité
- Infection (virale, bacterienne, fongique, parasites)
- Réaction immunologique (GvHD)
- Associé à la transfusion (TRALI)
- Hémorragie alvéolaire diffuse (DAH)
- Interstitial Pneumonitis précoce
- Est-ce que les poumons sont une cible de la GvHD?

Clinical Spectrum of lung disease after BMT



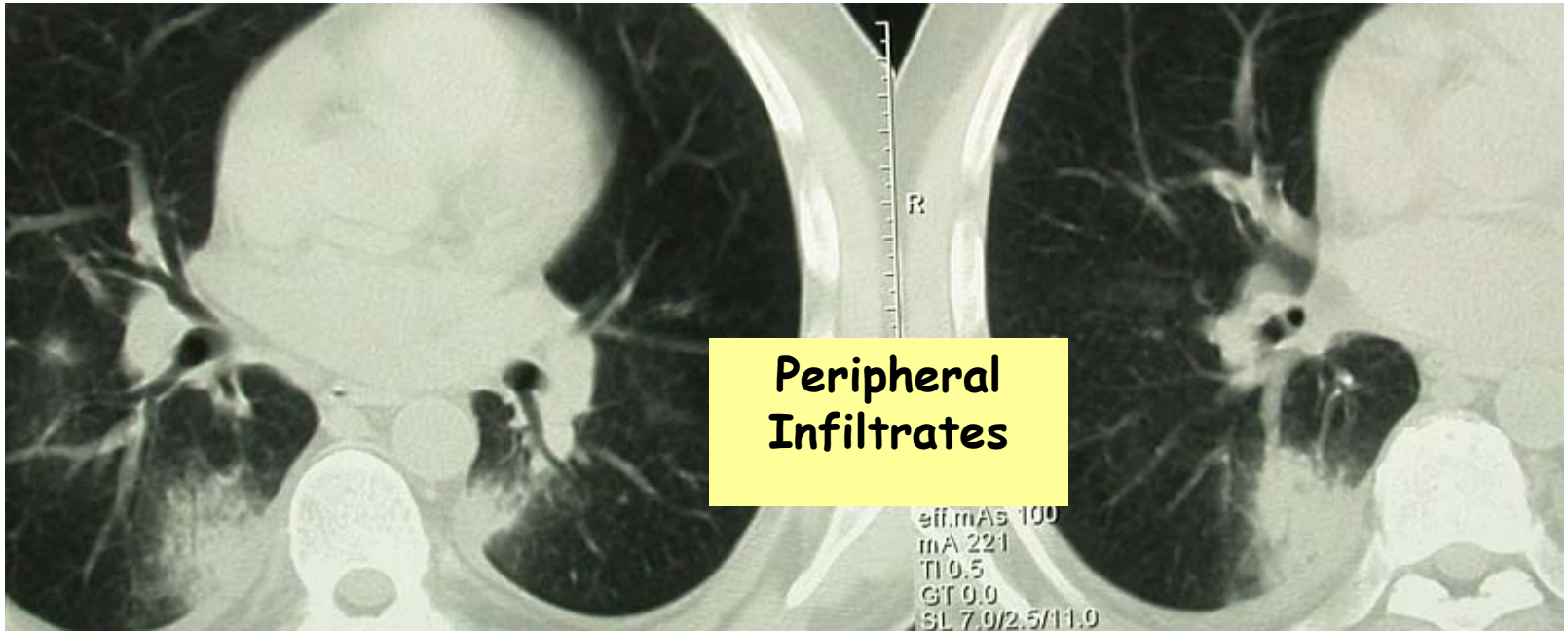






Vascular Invasion

Crescent Sign



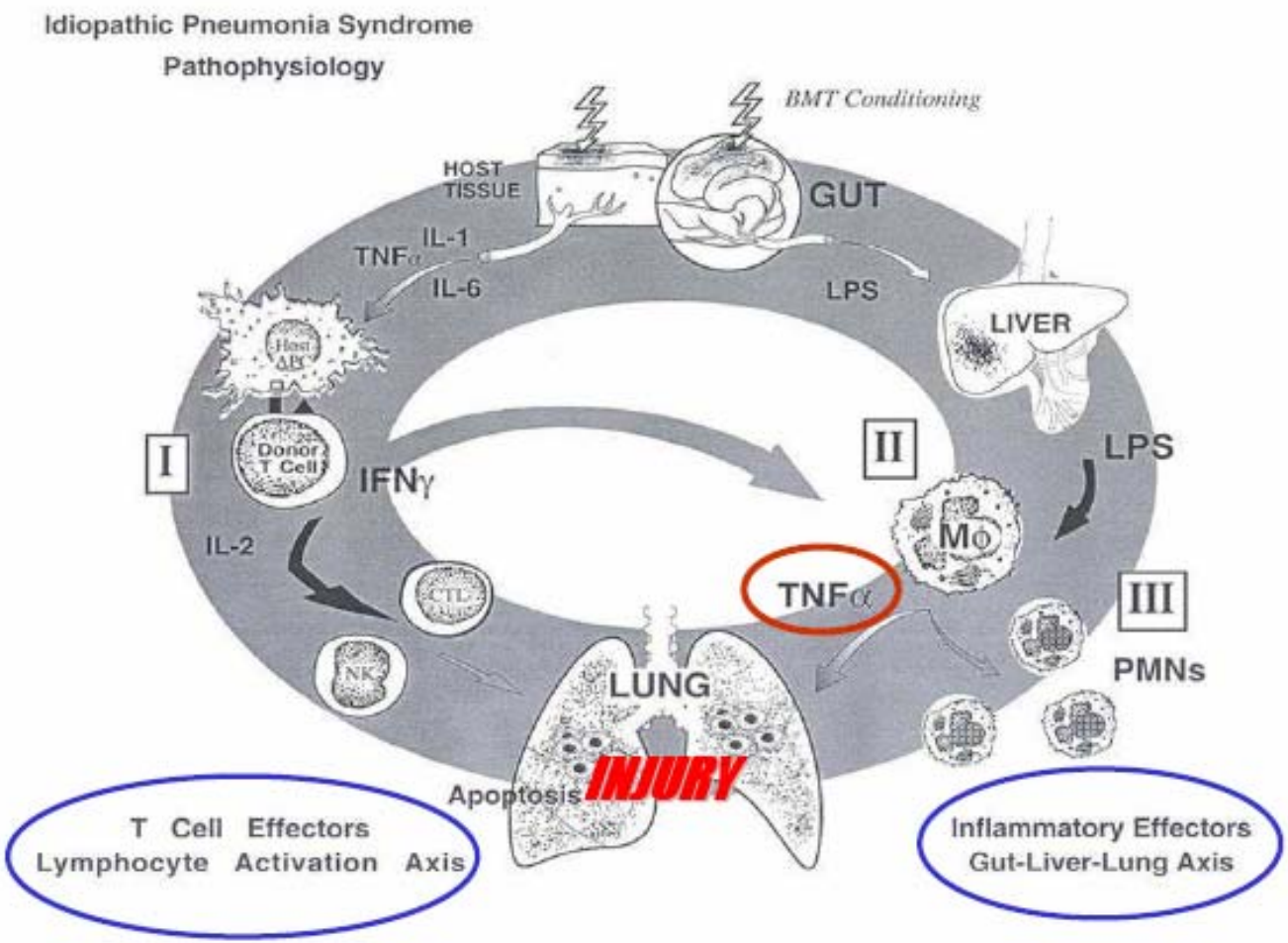
Peripheral Infiltrates

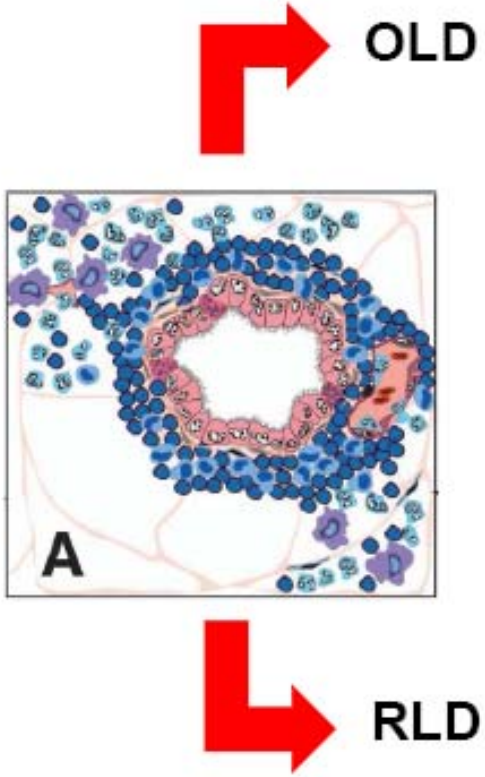
Pneumopathie
Interstitielle

CMV?
RSV?
Toxicité?

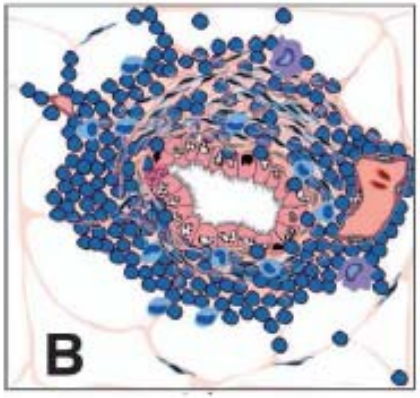
Pathophysiology of lung injury after BMT

"The Bench": A paradigm shift

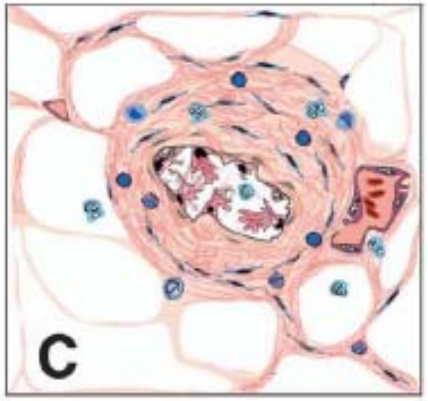




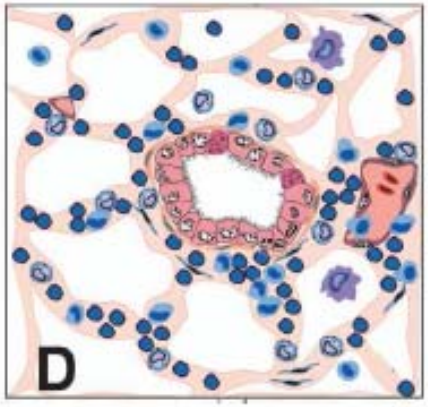
Chronic lymphocytic bronchiolitis



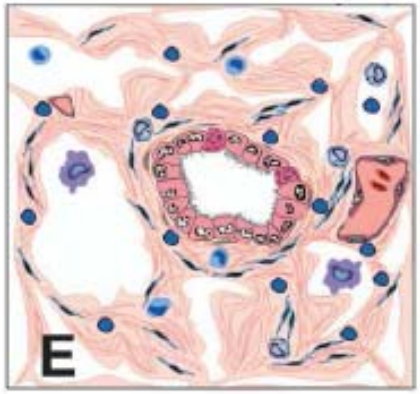
Bronchiolitis Obliterans (OLD)



Chronic interstitial pneumonitis



Restrictive Interstitial Fibrosis (RLD)



Phase one

acute inflammation

Phase two

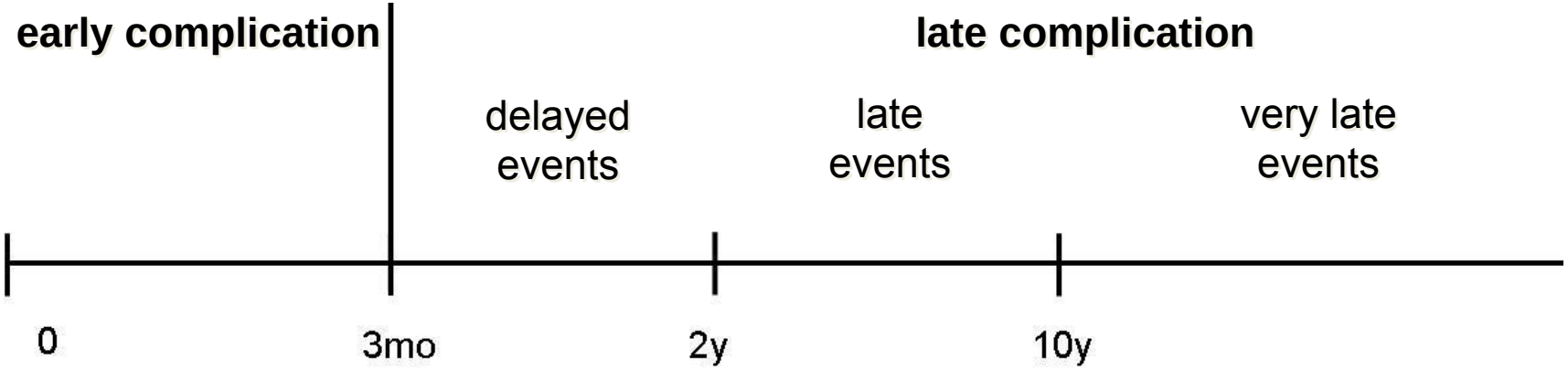
dysregulated repair

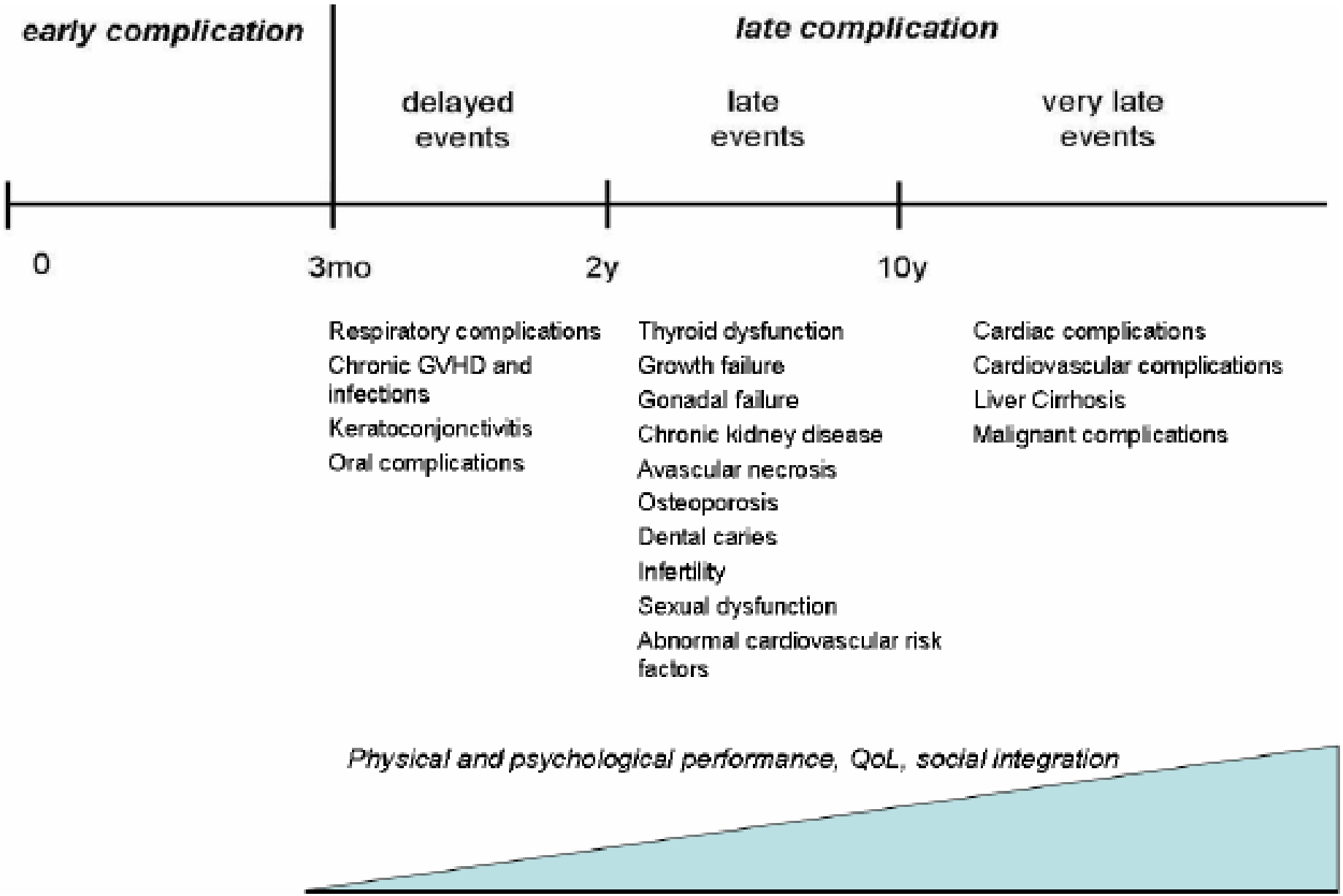
Phase three

collagen depo / fibrosis

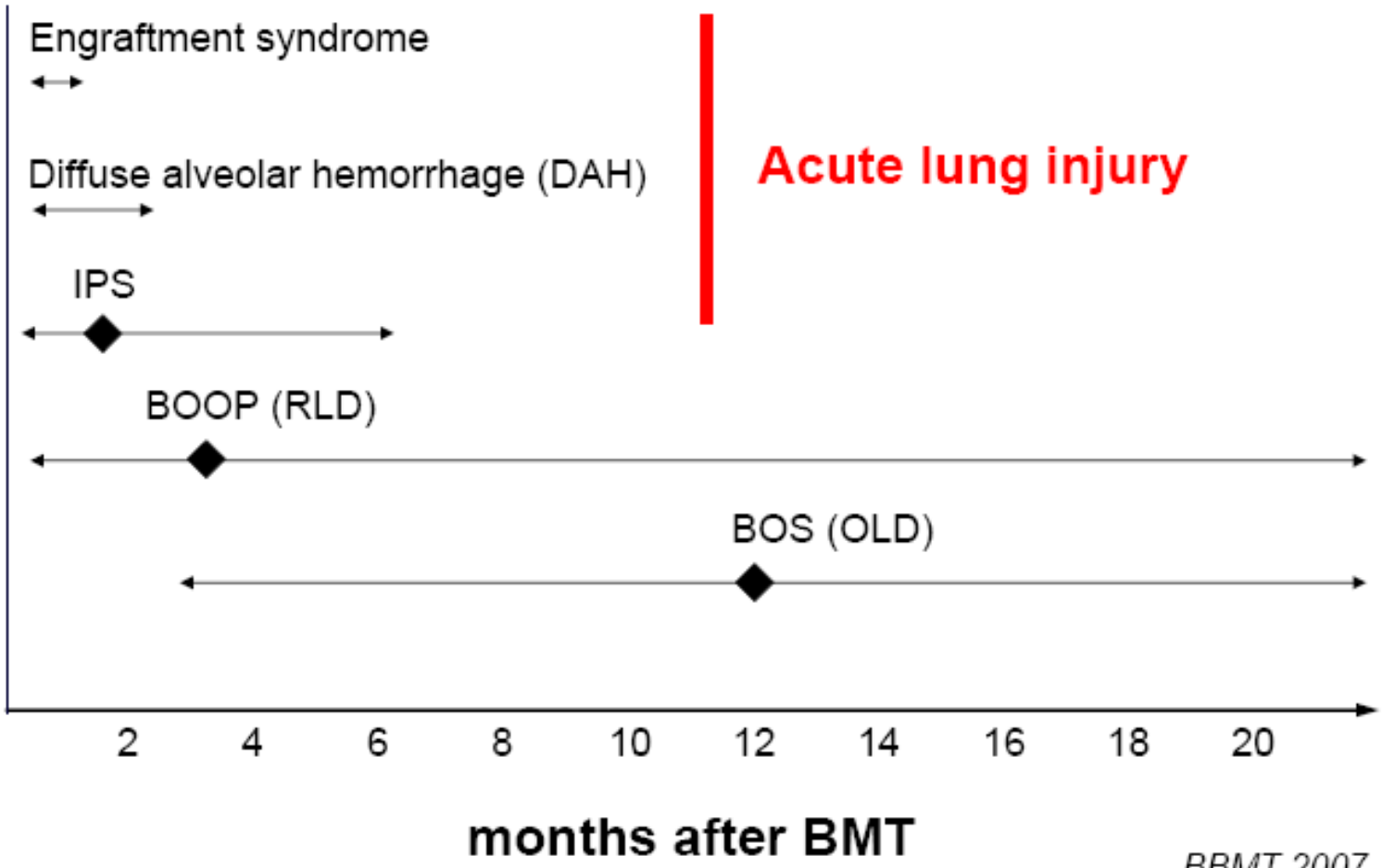
Late complications after HSCT

- Three characteristic courses of non-malignant complications
  - Clinical presentation
  - Time of appearance
  - Main risk factors
- Conditions appearing after early phase of HSCT with clinical consequences on the long term survivorship




early complication
late complication
delayed events
late events
very late events
0
3mo
2y
10y
Respiratory complications
Chronic GVHD and infections
Keratoconjonctivitis
Oral complications
Thyroid dysfunction
Growth failure
Gonadal failure
Chronic kidney disease
Avascular necrosis
Osteoporosis
Dental caries
Infertility
Sexual dysfunction
Abnormal cardiovascular risk factors
Cardiac complications
Cardiovascular complications
Liver Cirrhosis
Malignant complications
Physical and psychological performance, QoL, social integration

Time Course of Lung Injury after BMT



BBMT 2007

Case of Bronchiolitis Obliterans

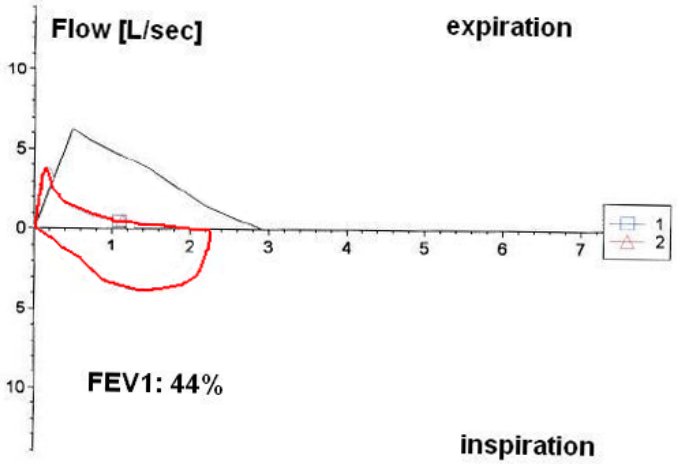
HSCT history

- 42-year old woman, AML
- Allogeneic HSCT in 2. CR, February 2006
- Unrelated matched donor
- AML in complete remission
- Complications
  - Acute GvHD grade II, skin and liver
  - Chronic extensive GvHD, skin and liver

Bronchiolitis obliterans

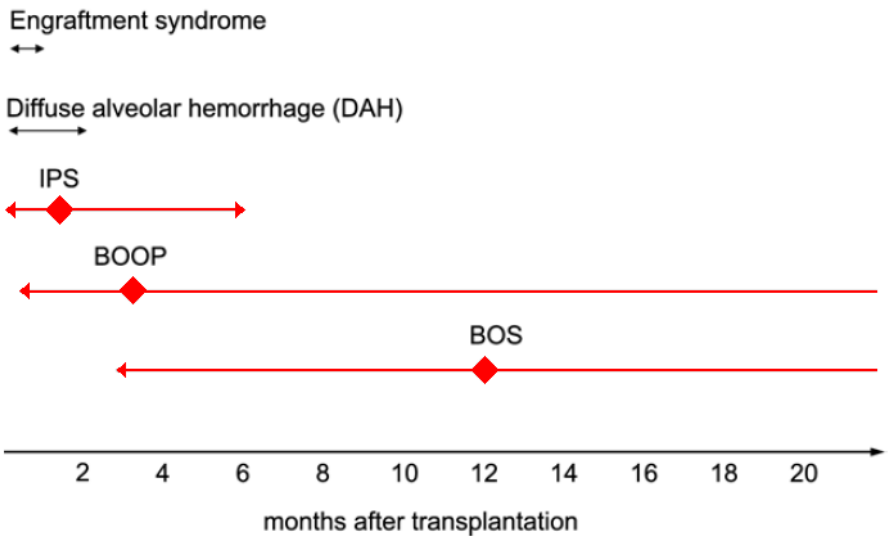
- First diagnosis, May 2006
- Relapsing pulmonary infections
- Pneumothorax twice
  - October 2007
  - January 2008

Flow-volume loop



Late pulmonary complications

- Involving both airway and lung parenchyma
- Infectious complications
- Non-infectious complications
  - Bronchiolitis obliterans (BO)
  - Bronchiolitis obliterans organizing pneumonia (BOOP)
  - Idiopathic pneumonia syndrome (IPS)
- Overlap between early and late complications



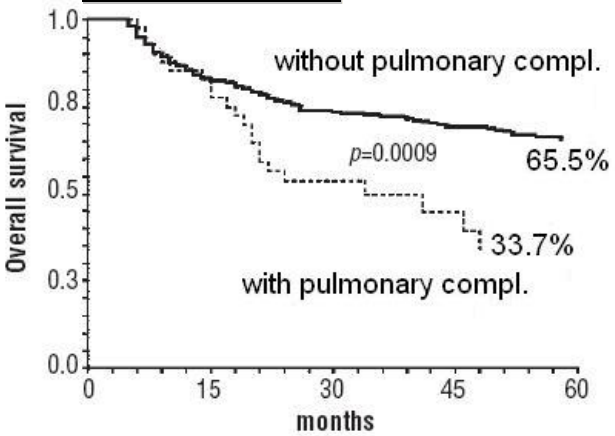
Yoshihara S et al. BBMT. 2007; 13:749-759

Outcome of late-onset of non-infectious pulmonary complications after HSCT

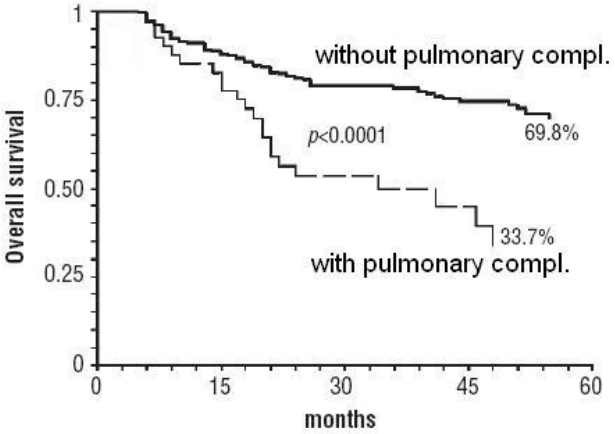
- Cumulative incidence of pulmonary complications
  - in 438 patients surviving > 3 months
  - 10% at 2 years

- Outcome of patients with pulmonary complications
  - 23/41 (56%) died
  - median follow-up: 14 months
  - 13 deaths due to respiratory failure

All patients

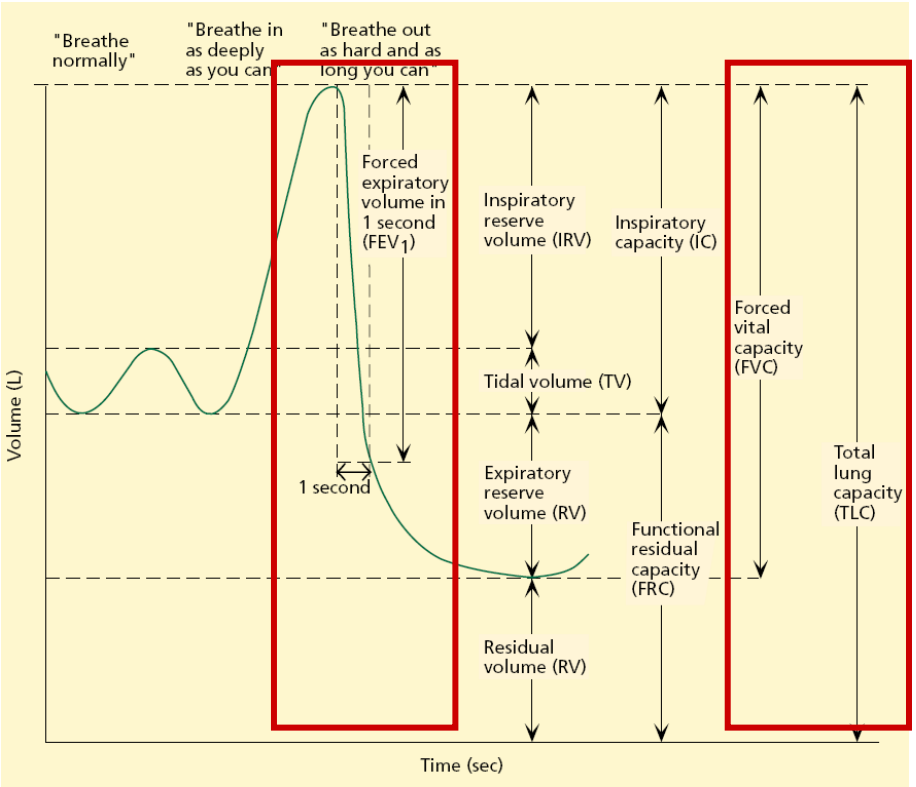


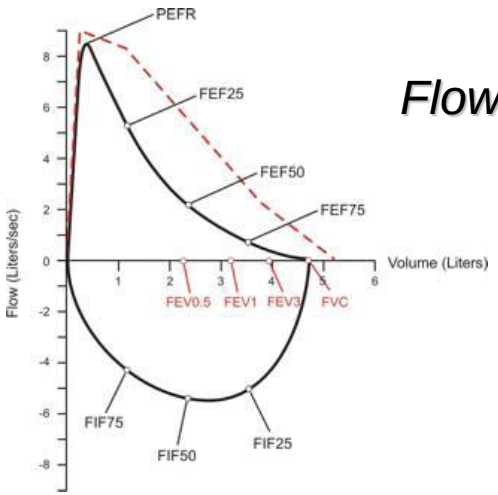
Only patients with cGvHD



Patriarca F. et al. Haematologica. 2006; 91:1268-1272

Pulmonary function tests





Flow-volume loop

Obstructive pattern	***Restrictive pattern***	***Parenchymal disease***
FEV1 ↘ FEV1/FVC ↘ FVC no TLC no	FEV1 no FEV1/FVC no FVC ↘ TLC ↘	DLCO ↘

Pulmonary function test pattern after HSCT

	Expiratory flow (FEV1/FVC)	Lung volume (TLC)	Gas transfer (DLCO)
Bronchiolitis obliterans	↘	normal	↘
Bronchiolitis obliterans organizing pneumonia	normal	↘	↘
Interstitial pneumonia syndrome	normal	↘	↘

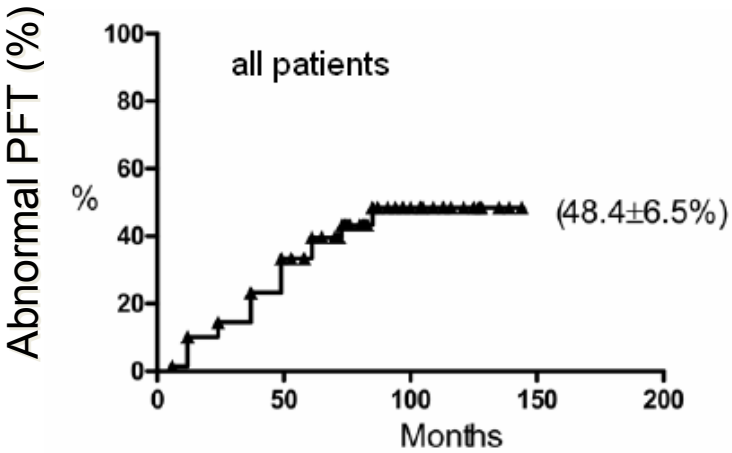
Table 2: Main characteristics of non-infectious delayed respiratory complications after hematopoietic stem cell transplantation

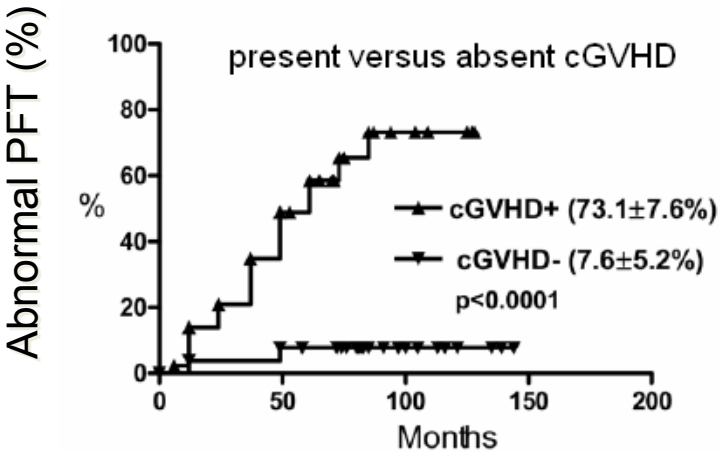
	Bronchiolitis obliterans (BO)	**Bronchiolitis obliterans organizing pneumonia (BOOP)**	**Idiopathic pneumonia syndrome (IPS)**
Pulmonary function tests	obstructive pattern	restrictive pattern	restrictive pattern
FEV1/FVC	decreased	normal	normal
TLC	normal	decreased	decreased
DLCO	decreased	decreased	decreased
CT scan	High resolution CT: in mosaic pattern on expirium, air trapping, bronchiectasis, bronchial wall thickening, centrilobular nodules	Consolidation, ground glass opacity, nodules	presence of multilobar infiltrates
Bronchoscopy	transbronchial biopsy contraindicated (risk of pneumothorax)	to rule out an infection	to rule out an infection
Biopsy	dense eosinophilic scarring beneath the respiratory epithelium, resulting in complete fibrous obliteration or some degree of luminal narrowing	plugs of granulation tissue that fill the lumens of the distal airways in a patchy distribution, extending into the alveolar ducts and alveolar sacs, and associated with chronic interstitial inflammation	severe pulmonary fibrosis, diffuse alveolar damage, interstitial lymphocytic infiltration

FEV1: forced expiratory volume in 1 second; FEVC: forced vital capacity; TLC: total lung capacity; DLCO: carbon monoxide lung diffusion capacity;

Pulmonary function tests (PFT) after allogeneic HSCT

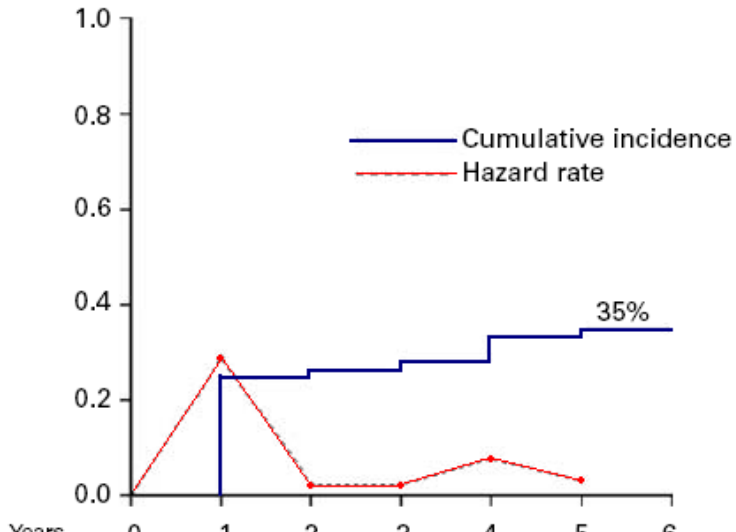
- 69 patients with 5-year follow-up
- Decrease in PFT in 31/69 (44%) patients
  - 25 restrictive pattern
  - 6 obstructive pattern
- Symptomatic patients
  - 12/31 (38%)
- Risk factors
  - Chronic GVHD
  - Abnormal PFT before HSCT



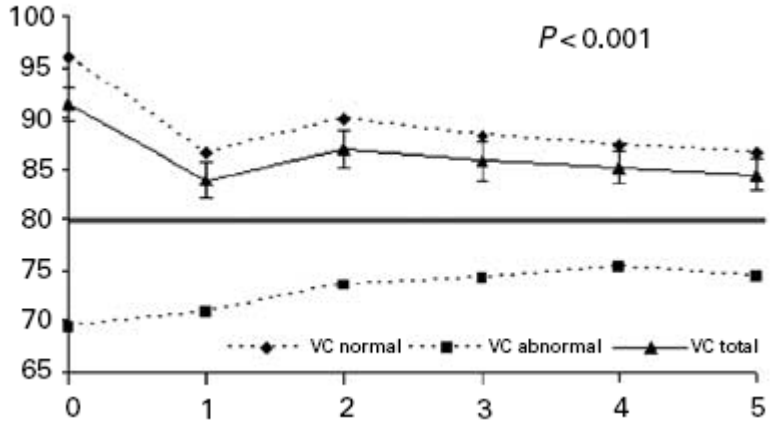


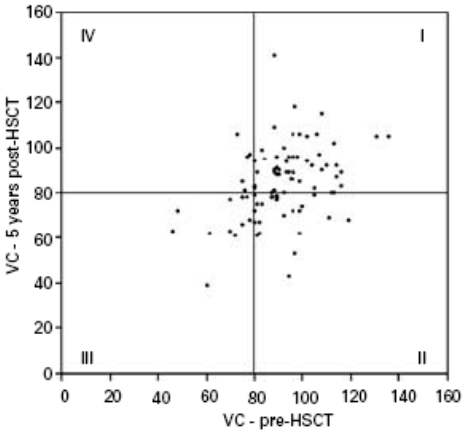
Savani B. et al. BBMT. 2006; 12:1261-1269

Prospective long-term follow-up of PFT in children after allogeneic HSCT



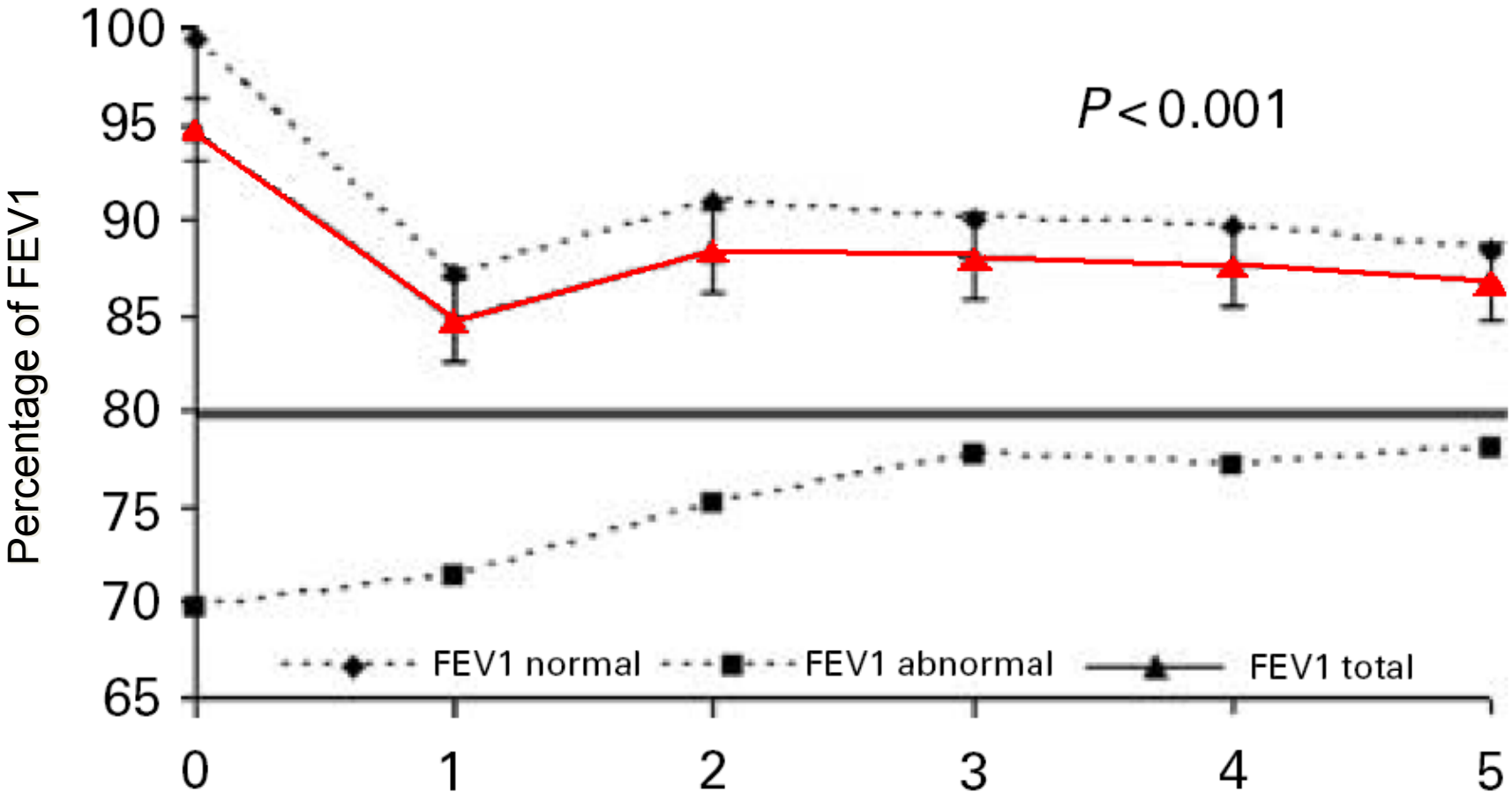
Years	0	1	2	3	4	5	6
N of patients	78	78	74	69	69	69	
Cumulative incidence	0%	25%	26%	28%	33%	35%	
Hazard rate	0	0.29	0.02	0.02	0.07	0.03	





Uderzo C. et al. BMT. 2007; 39:667-675

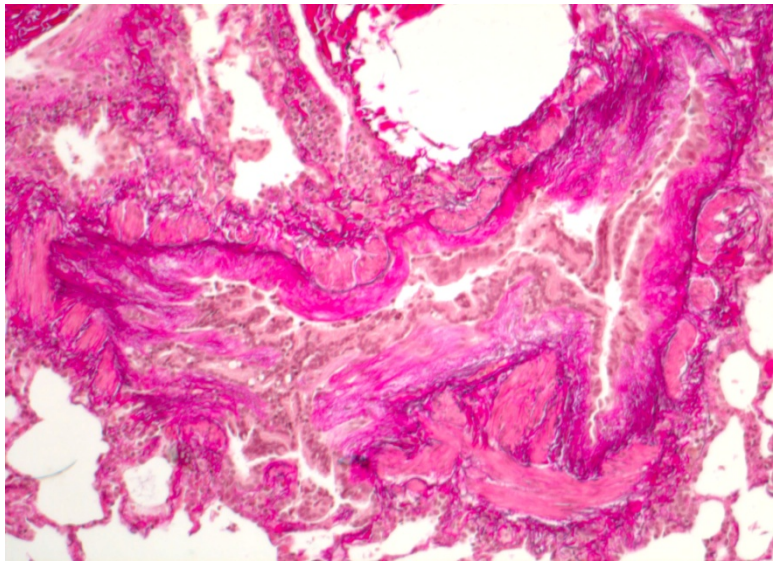
Prospective long-term follow-up of PFT in children after allogeneic HSCT



Uderzo C. et al. BMT. 2007; 39:667-675

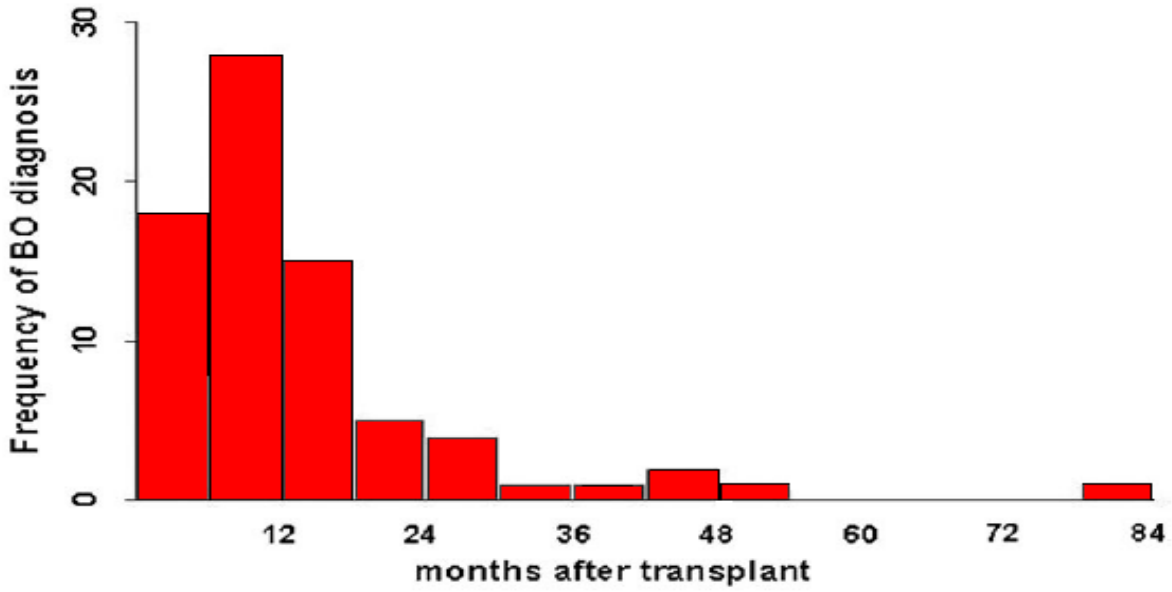
Bronchiolitis Obliterans (BO)

- Severe pulmonary manifestation
  - Non-specific inflammatory injury
  - Affecting primarily the small airways
- At initial stage
  - Mainly an obstructive disease
- At more advanced stage
  - progressive peribroncheolar fibrosis



Incidence and Time of Onset

- Incidence rate
  - Broad ranges between studies
  - Among 2152 patients from 9 studies, median incidence of 8.3%
  - Among 6’275 patients from the CIBMTR, 76 patients (1.7%)



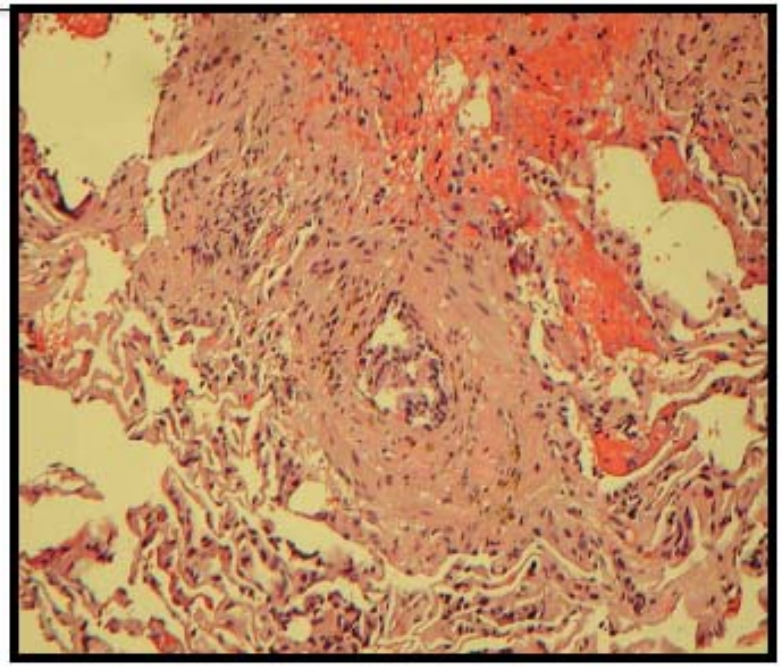
Afessa B et al. Review. BMT. 2001; 28:425-434
Santo T. et al. Chest. 2005;126:153-161

Bronchiolitis Obliterans Syndrome (BOS)

Obstrucive (OLD)

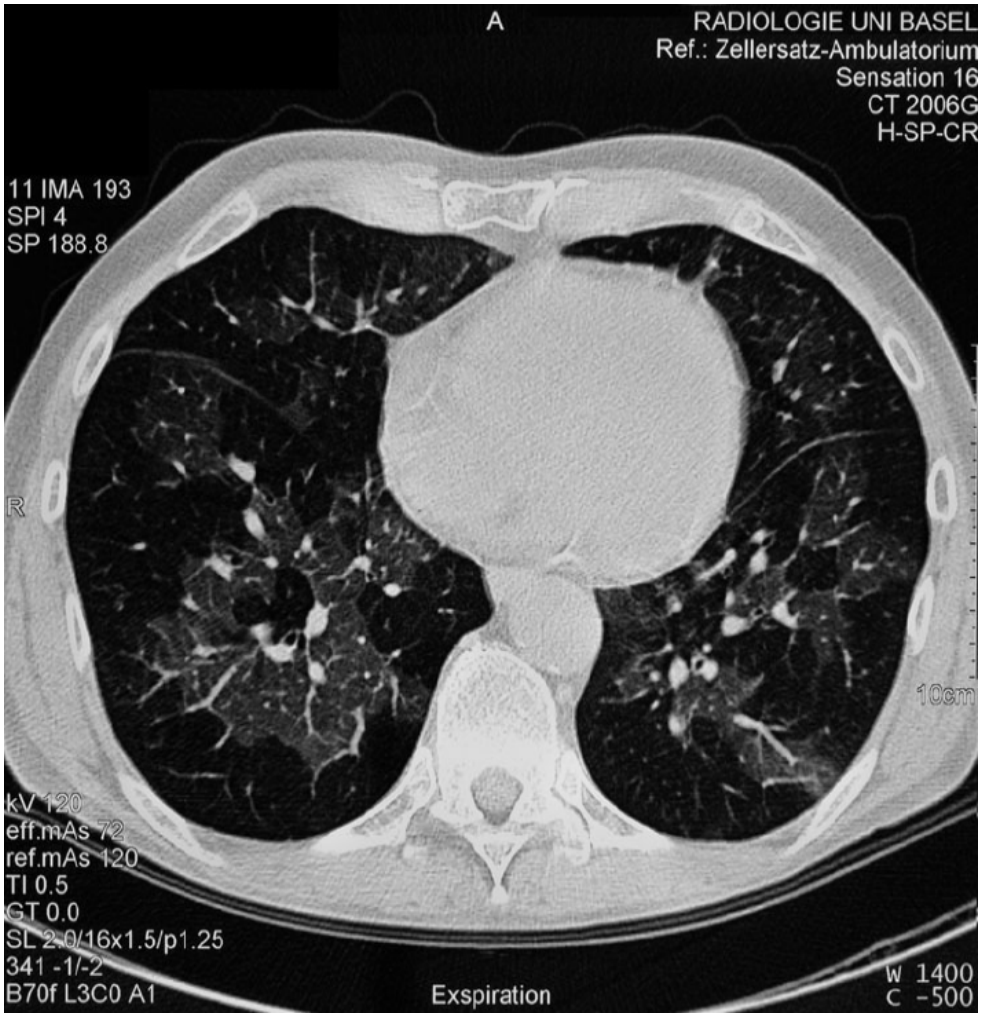
LUNG MECHANICS		Actual	Baseline Pred	%Pred
FVC	liters	1.61	4.30	**37%**
FEV1	liters	0.64	3.24	**20%**
FEV1/FVC	%	40%	75%	**53%**
FEFMAX	l/sec	3.95	8.55	**46%**
FEF25-75	l/sec	0.20	3.41	**6%**
FEF25	l/sec	0.44	7.71	**6%**
FEF50	l/sec	0.22	5.22	**4%**
FEF75	l/sec	0.07	2.32	**3%**
FIVC	liters	1.01	4.30	**24%**
FIFMAX	l/sec	1.96	8.55	**23%**
FIF50	l/sec	1.85	5.22	**35%**
FEF50/FIF50	%	12%	100%	**12%**

Pathology



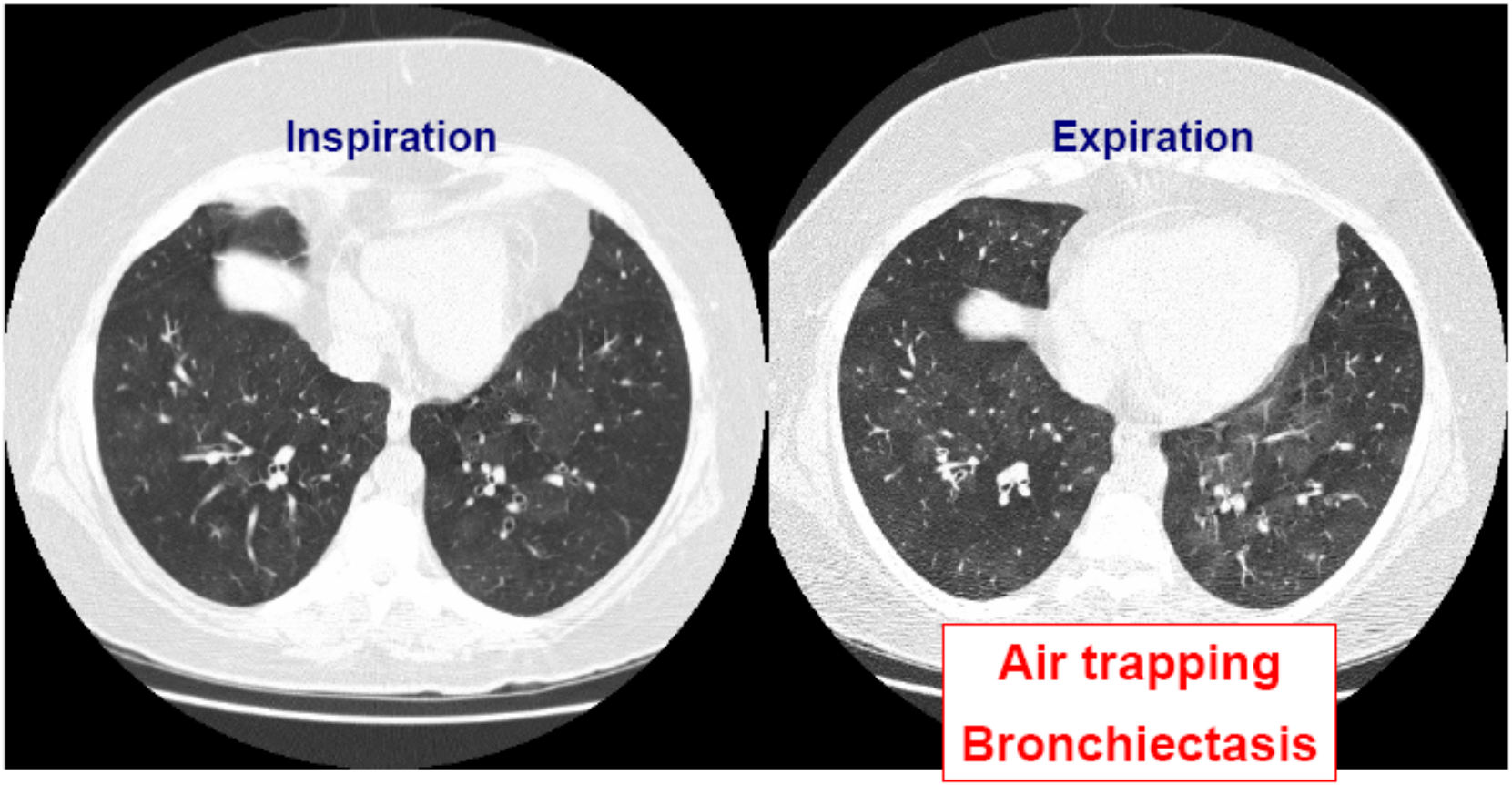
Clinical presentation of BO

- Insidious
- Dry cough, progressive dyspnoe, wheezing
- No fever
- Asymptomatic presentation with abnormal PFT in 20% of the cases
- At more advance phase
  - Evidence of hyperinflation
- Pulmonary function tests



Bronchiolitis Obliterans Syndrome (BOS)

Chest CT findings



Risk Factors for Bronchiolitis Obliterans

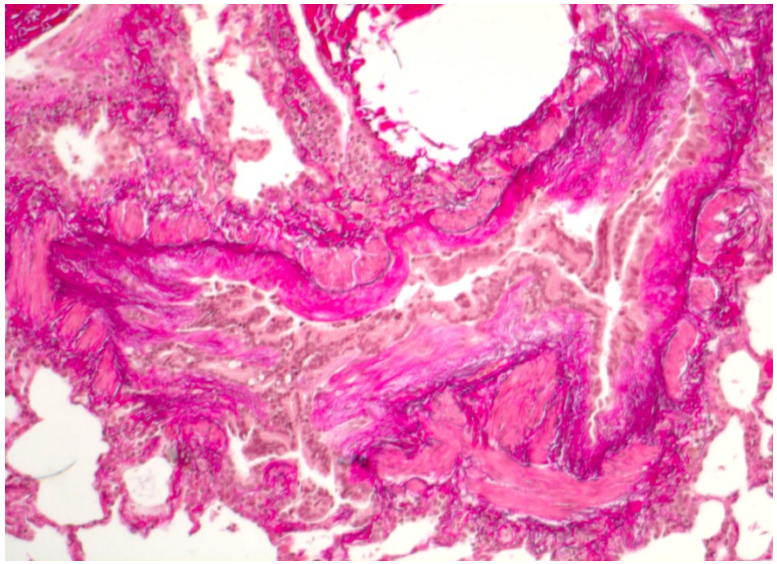
- Strong association with chronic GvHD
  - BO is considered a manifestation of GvHD
  - Few cases of BO in autologous HSCT

Risk factors	HR	95% CI	P Value
Busulfan based conditioning	2.24	1.4 -3.6	0.0009
Time from diagnosis (>14 months)	1.93	1.2 – 3.07	0.0053
Peripheral blood	3.35	1.8 – 6.3	0.0002
Female donor into male recipient	1.78	1.1 – 2.8	0.0152
Acute GvHD Grade ≥II	2.12	1.3 – 3.4	0.0014
Interstitial pneumonitis	2.28	1.3 – 3.9	0.0029

Santo T. et al. Chest. 2005;126:153-161

Chronic GvHD of the Lung and Bronchiolitis Obliterans

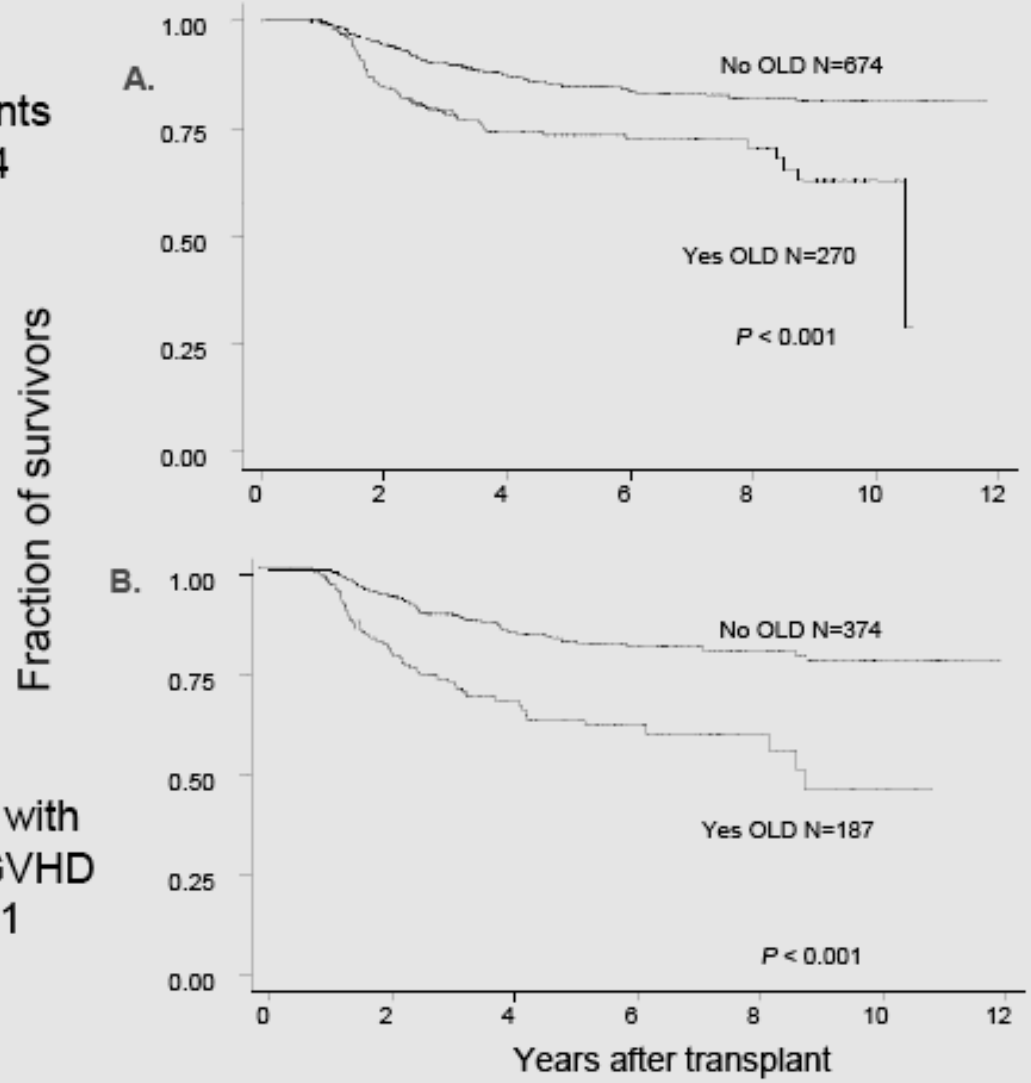
- Biopsy proven BO
  - is the only diagnostic manifestation of chronic GVHD
- Clinically diagnosis of BO
  - FEV1/FVC ration <75% of predicted
  - Evidence of air trapping or small airway thickening, or bronchectasis on HRCT
  - Absence of infection in the respiratory tract



Filipovich A. et al. BBMT. 2005;11:945-955.

Influence of OLD on mortality after BMT

All patients
N=944



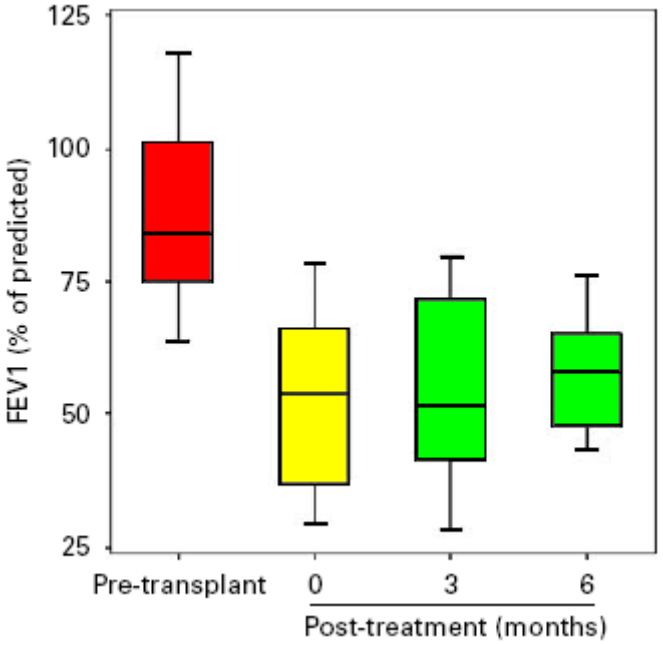
Patients with
chronic GVHD
N=561

Chien et. al
BMT: 2004
AJRCCM: 2003

Therapeutic Recommendations

- No prospective studies available
- Treatment of infections
- Treatment of chronic GvHD
- Fractionated TBI instead of single dose TBI
- Systemic steroids
  - 1-2mg/kg/day
  - for 2-6 weeks
- Inhaled steroids with bronchiodilatators

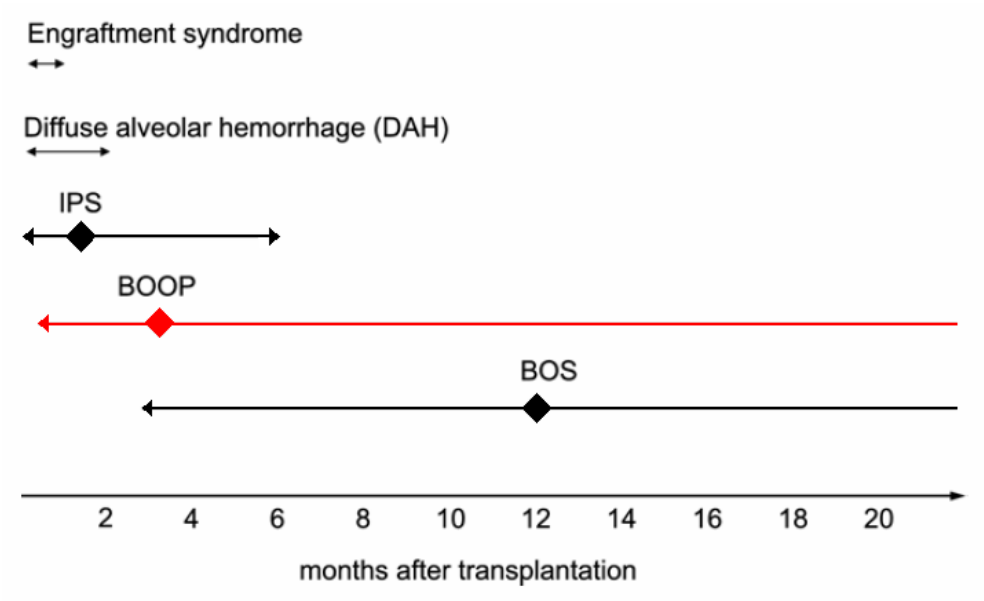
Inhaled steroids with bronchiodilatators



Bashoura L. et al. BMT. 2008;41:63-67.

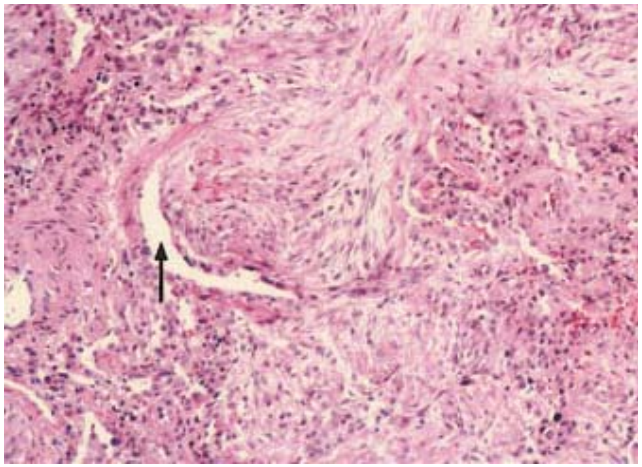
Bronchiolitis Obliterans Organizing Pneumonia; Cryptogenic Organizing Pneumonia (COP)

- Clinicopathological syndrome involving
  - Bronchioles, alveolar ducts, and alveoli
  - Lumen of the alveoli filled with granulation tissue
- In HSCT presents as an interstitial pneumonia rather than an airway disease



Clinical presentation of BOOP/COP

- Acute onset of dry cough, dyspnea and fever
- Chest X-ray
  - Peripheral patchy consolidation
- Pulmonary function
  - Restrictive pattern with FVC & DLCO ↘
- Bronchoscopy with BAL to rule out infection
- Diagnosis proven by lung histology



- In a retrospective biopsy review
- 817 surgical lung biopsy after HSCT
- 49 cases of histology proven BOOP/COP
- In a case control study with 161 controls
- All BOOP/COP cases related with acute or chronic GVHD
- 78% remained stable, 22% were progressive,
- 5-year survival 33%
- 8/11 with progressive disease died

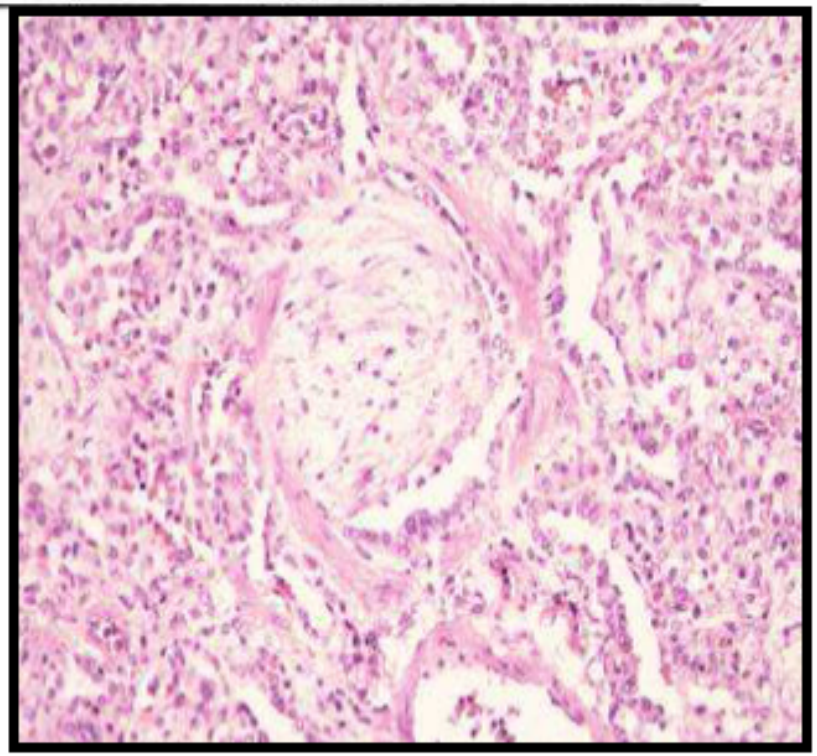
Freudenberger T. et al. Blood. 2003;102:3822-3828.

Bronch Obliterans Organizing Pneumonia (BOOP)

Restrictive (RLD)

LUNG MECHANICS		Baseline Actual	Baseline Pred	Baseline %Pred
FVC	liters	2.39	3.34	**72%**
FEV1	liters	1.80	2.53	**71%**
FEV1/FVC	%	75%	76%	**99%**
FEFMAX	l/sec	6.05	6.11	**99%**
FEF25-75	l/sec	1.40	2.89	**48%**
FEF25	l/sec	3.06	5.60	**55%**
FEF50	l/sec	1.69	4.24	**40%**
FEF75	l/sec	0.60	1.96	**31%**
FIVC	liters	2.48	3.34	**74%**
FIFMAX	l/sec	4.95	6.11	**81%**
FIF50	l/sec	4.77	4.24	**112%**
FEF50/FIF50	%	35%	100%	**35%**
MVV	l/min	98	98	**100%**

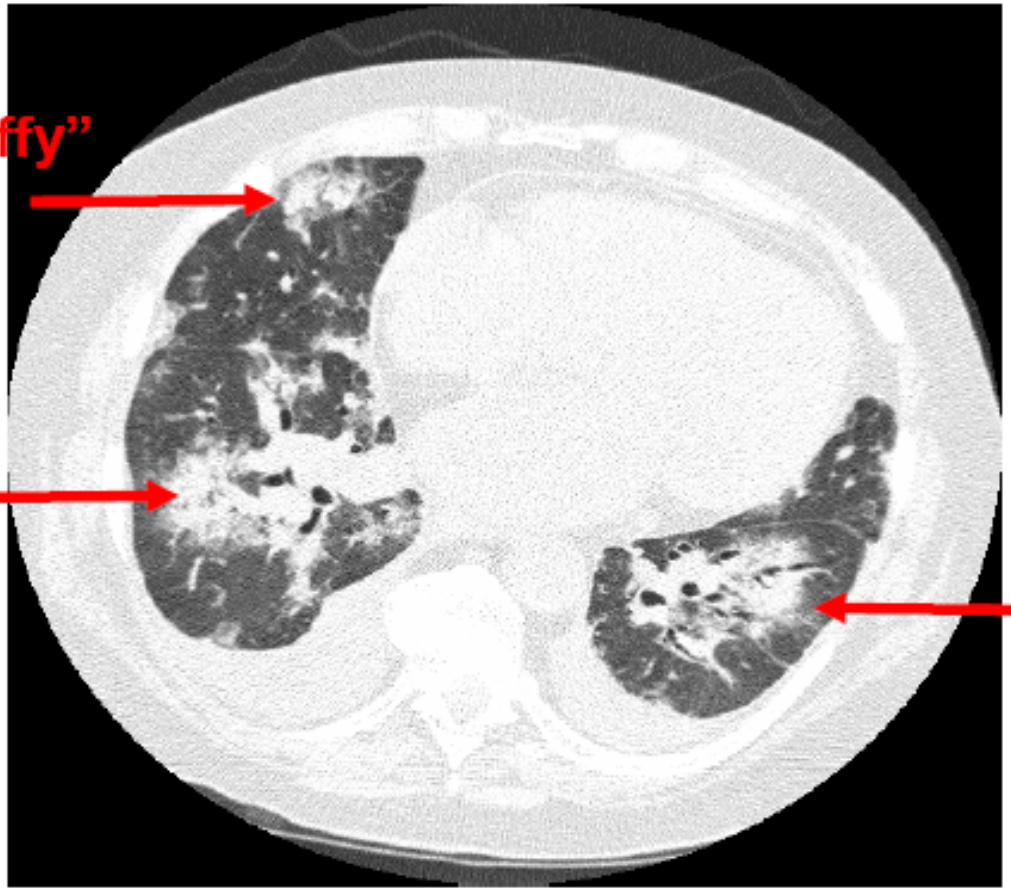
Pathology



Bronch Obliterans Organizing Pneumonia (BOOP)

Chest CT findings

Patchy "fluffy" Infiltrates



BOS and BOOP are distinct entities!

	BOS	BOOP
Symptoms	Progressive dyspnea	Dyspnea
	Non productive cough	Non productive cough
	Typically afebrile	Fever
Physical exam.	Wheezing	Rales
Time of Onset	Late (6 to 18 months)	Early (3 to 6 months)
Response to Tx	More likely	Less Likely
PFT	Obstructive lung disease	Restrictive lung disease
FEV1/FVC	Decreased	Normal
TLC	Normal	Decreased
DLCO	Decreased	Decreased
Radiology	Air trapping (exp phase)	"Fluffy" Consolidation
CT scan	Mosaic perfusion	Ground glass opacities
	Bronchiectasis	
	Bronchial wall thickening	
	Centrilobular nodules	

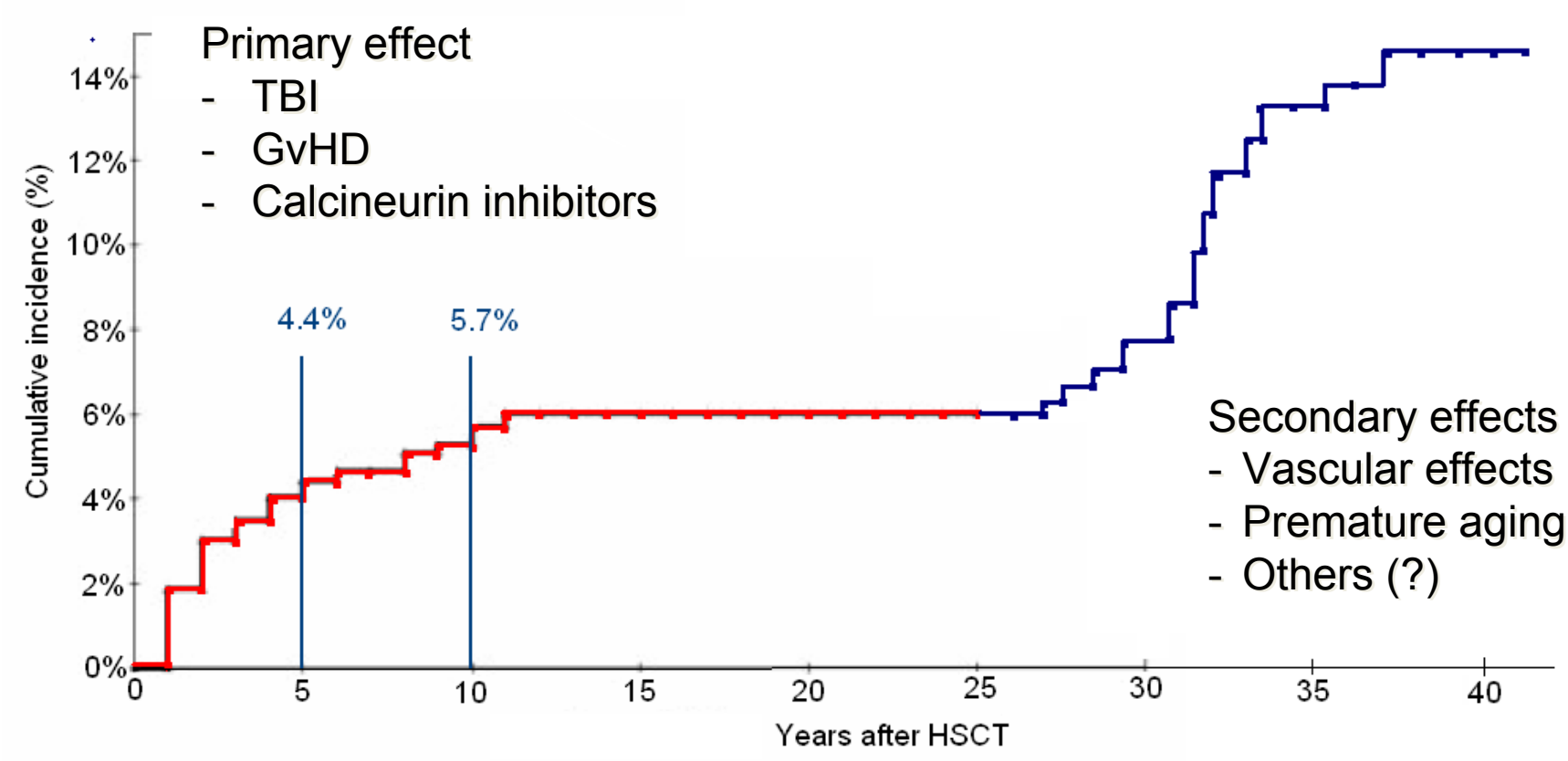
Satoshi Yoshihara,[1] Gregory Yanik,[2] Kenneth R. Cooke,[2] Shin Mineishi[1] BBMT 2007

Chronic Lung Injury after Allogeneic BMT

Treatment Strategies

- Association between OLD and cGVHD → immune mediated; less so for RLD
- "Standard" therapy for OLD generally includes:
  - ↑ immuno-suppression, anti-microbial prophylaxis bronchodilator therapy, supportive care
- No drug or combination of drugs has been found particularly efficacious
- Few clinical trials → even fewer randomized studies
- Responses tend to occur early
  - early Dx may be key: by PFTs or other risk factors
- Possible novel agents:
  - inhaled CSA, azithromycin, etanercept, ECP, pentostatin

Hyothetical cumulative incidence of the very long term?



25 ans

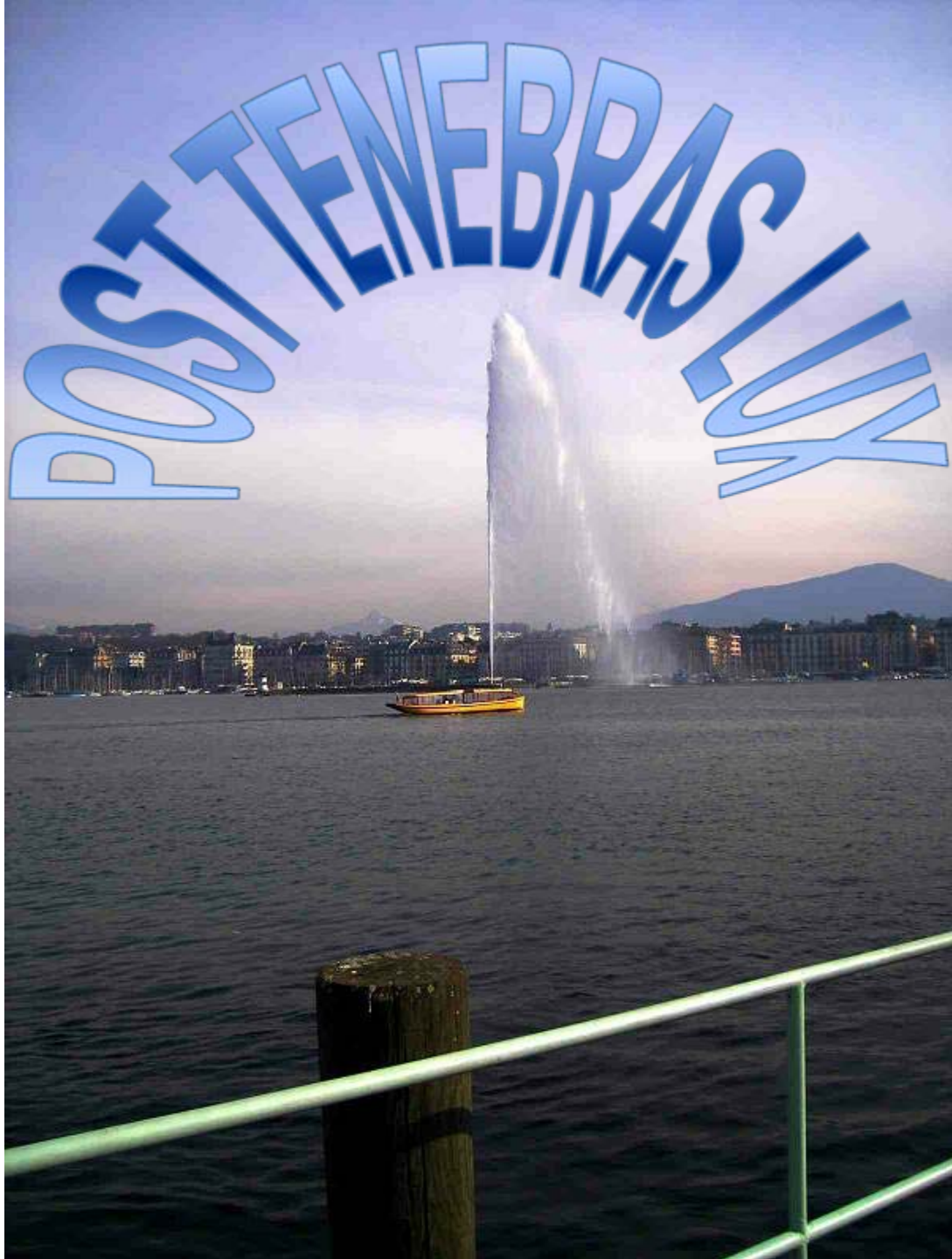
de transplantation allogénique de moelle osseuse aux Hôpitaux Universitaires de Genève

HUG
Hôpitaux Universitaires de Genève

25 de greffe aux HUG

500 UPN

1000 Cord Blood units in the Bank



Bronch Obliterans Organizing Pneumonia (BOOP)

Association between acute and chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia in recipients of hematopoietic stem cell transplants

Todd D. Freudenberger, David K. Madtes, J. Randall Curtis, Peter Cummings, Barry E. Storer, and Robert C. Hackman

- **Case controlled study of patient with *histologic* BOOP**
- **Characteristics of disease resembled idiopathic BOOP**
- **Incidence of 1%; median time to Dx: ~110 days after BMT**
- **Strong association with prior GVHD (acute & chronic)**
- **Patients with BOOP were more likely to have**
  - **high grade acute GVHD (skin)**
  - **chronic GVHD (gut and oral cavity) → progressive / extensive**
- **BOOP resolved or remained stable in 78% of patients**

Freudenberger, 2003: *Blood*