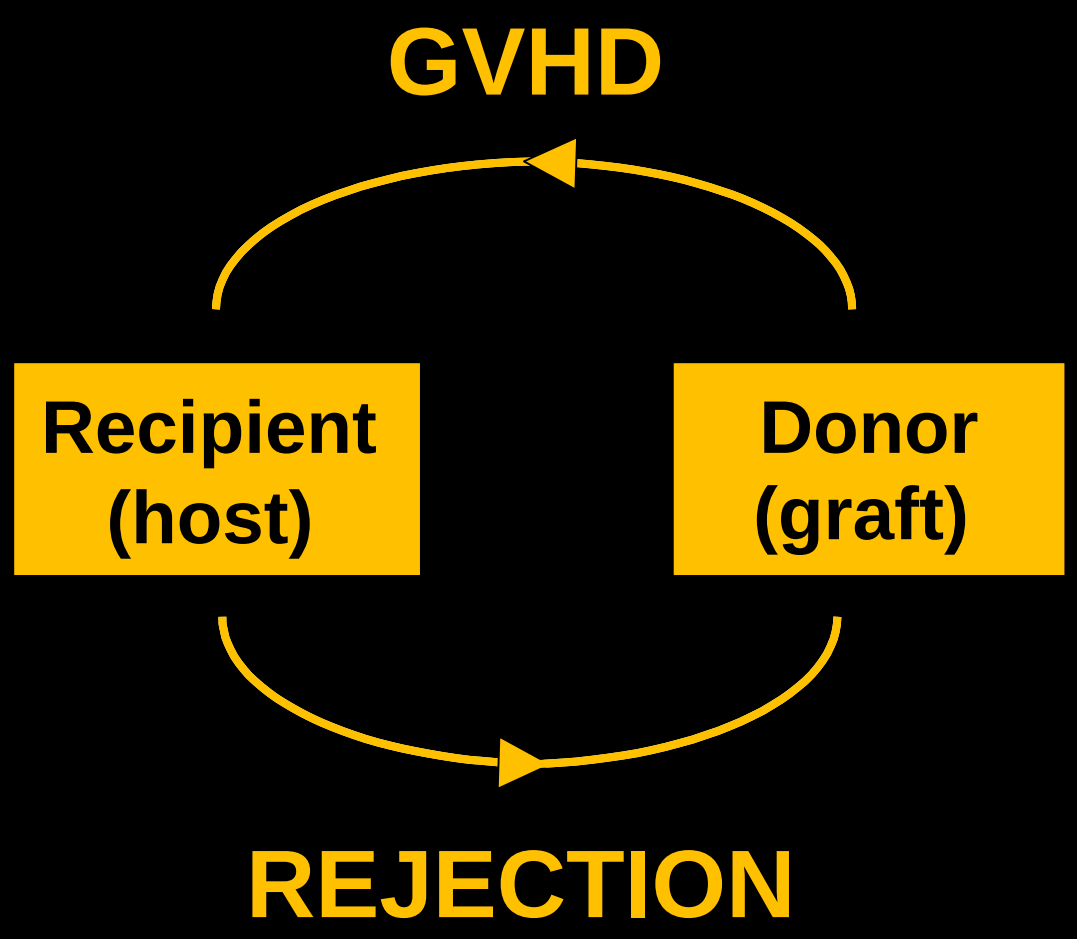
GVHD

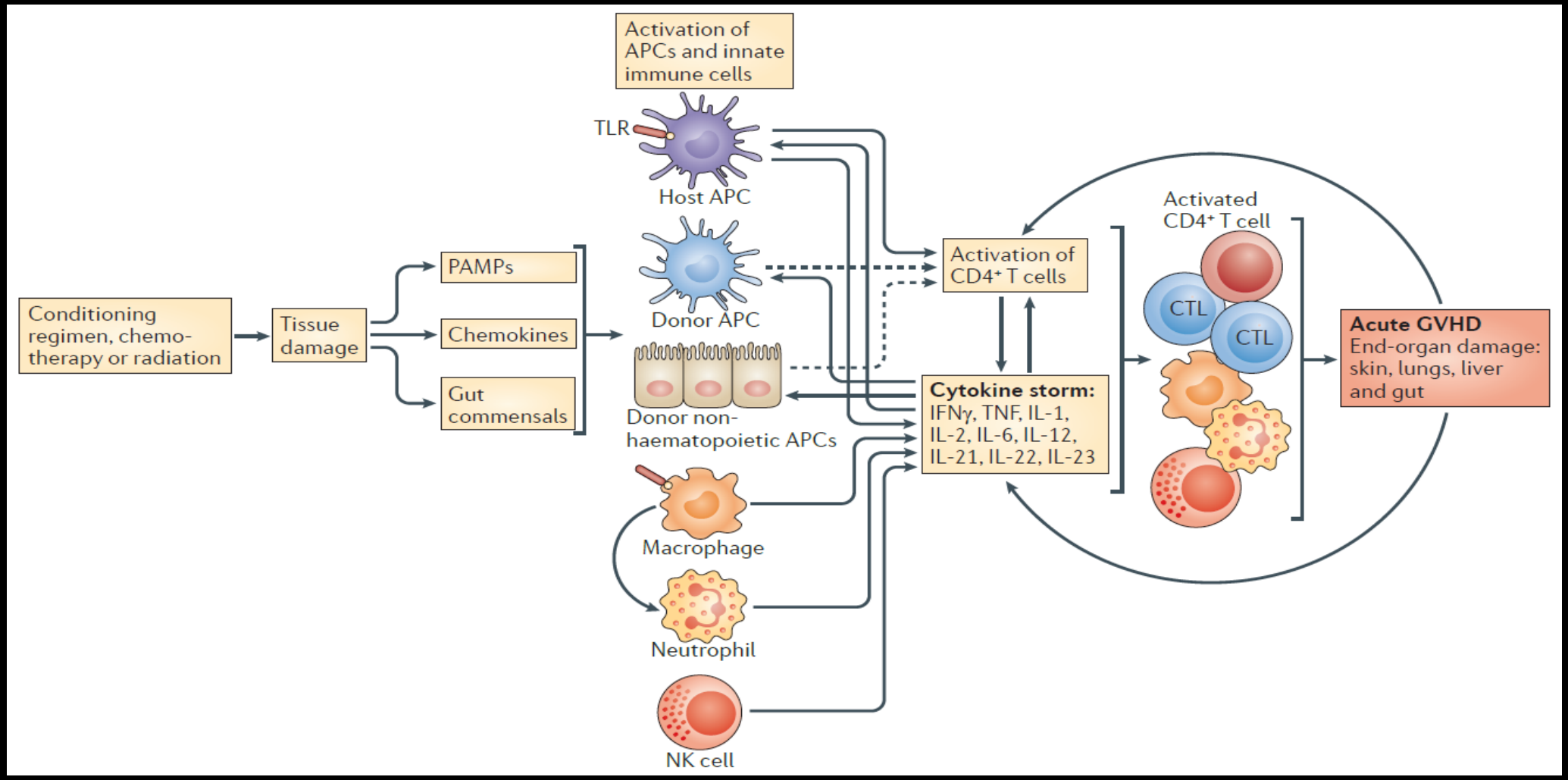
HCT

Rejection and graft-vs-host disease (GVHD)



GVHD

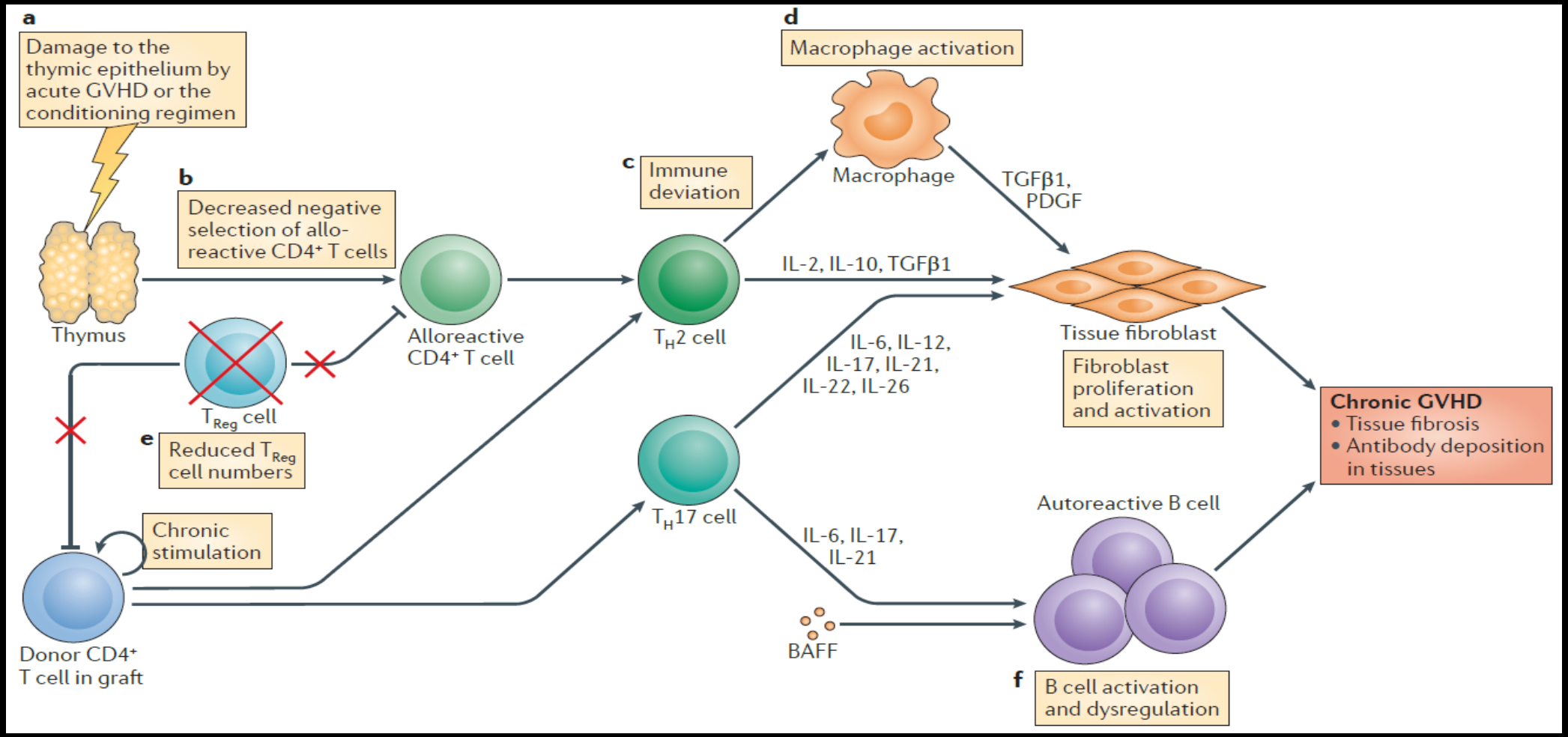
Acute GVHD : pathogenesis



Blazar et al, Nature Rev Immunol 12: 443-458,2012

GVHD

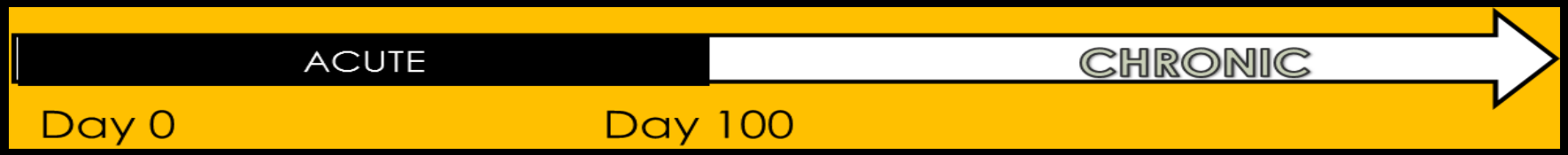
Chronic GVHD : pathogenesis

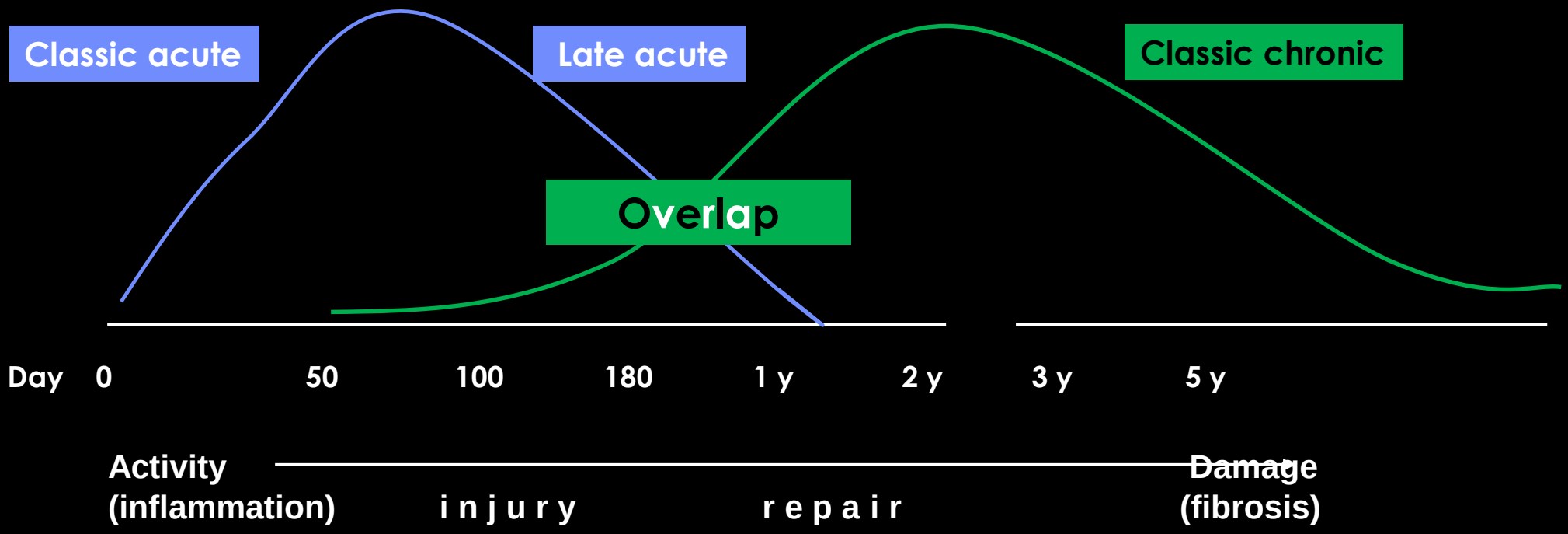


Blazar et al, Nature Rev Immunol 12: 443-458,2012

GVHD

GVHD : categories

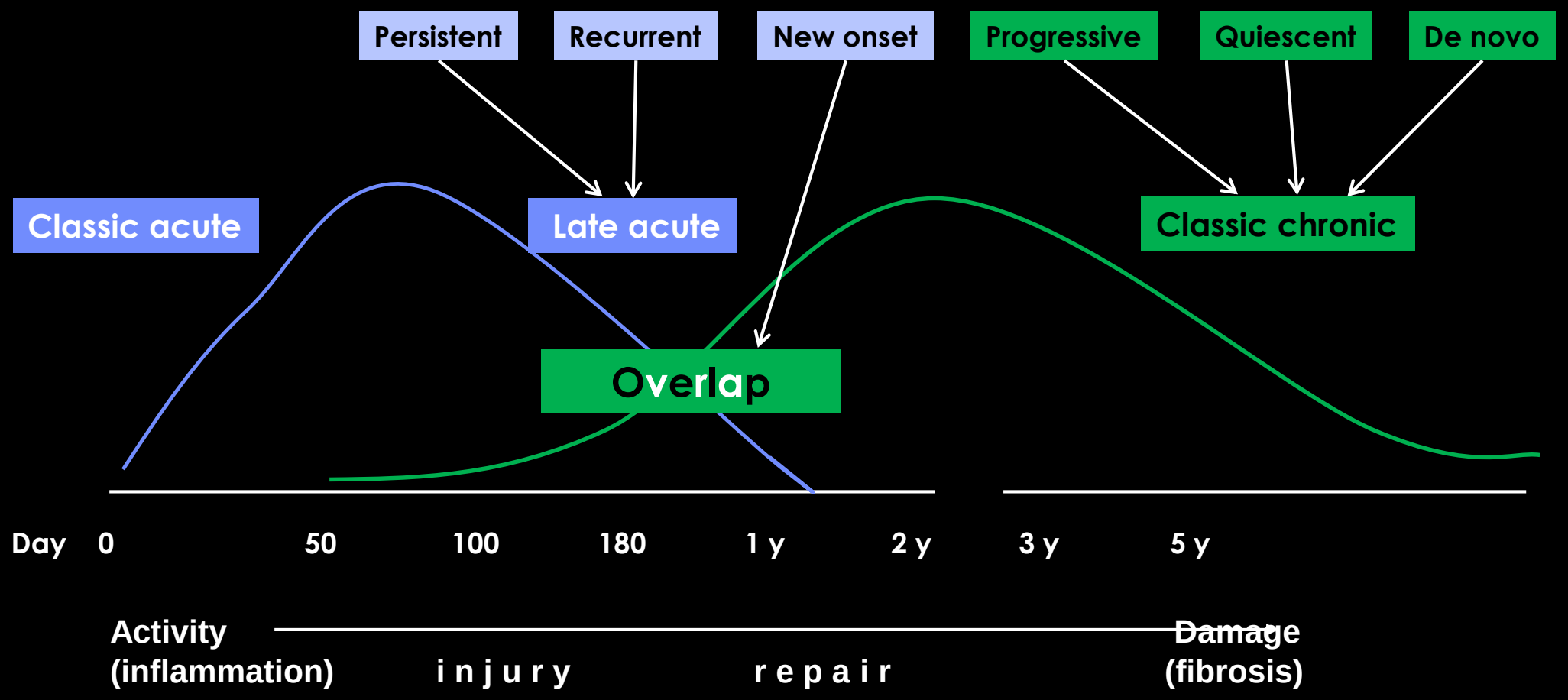




Carpenter & Greinix & Schoemans 2014

GVHD

GVHD : categories



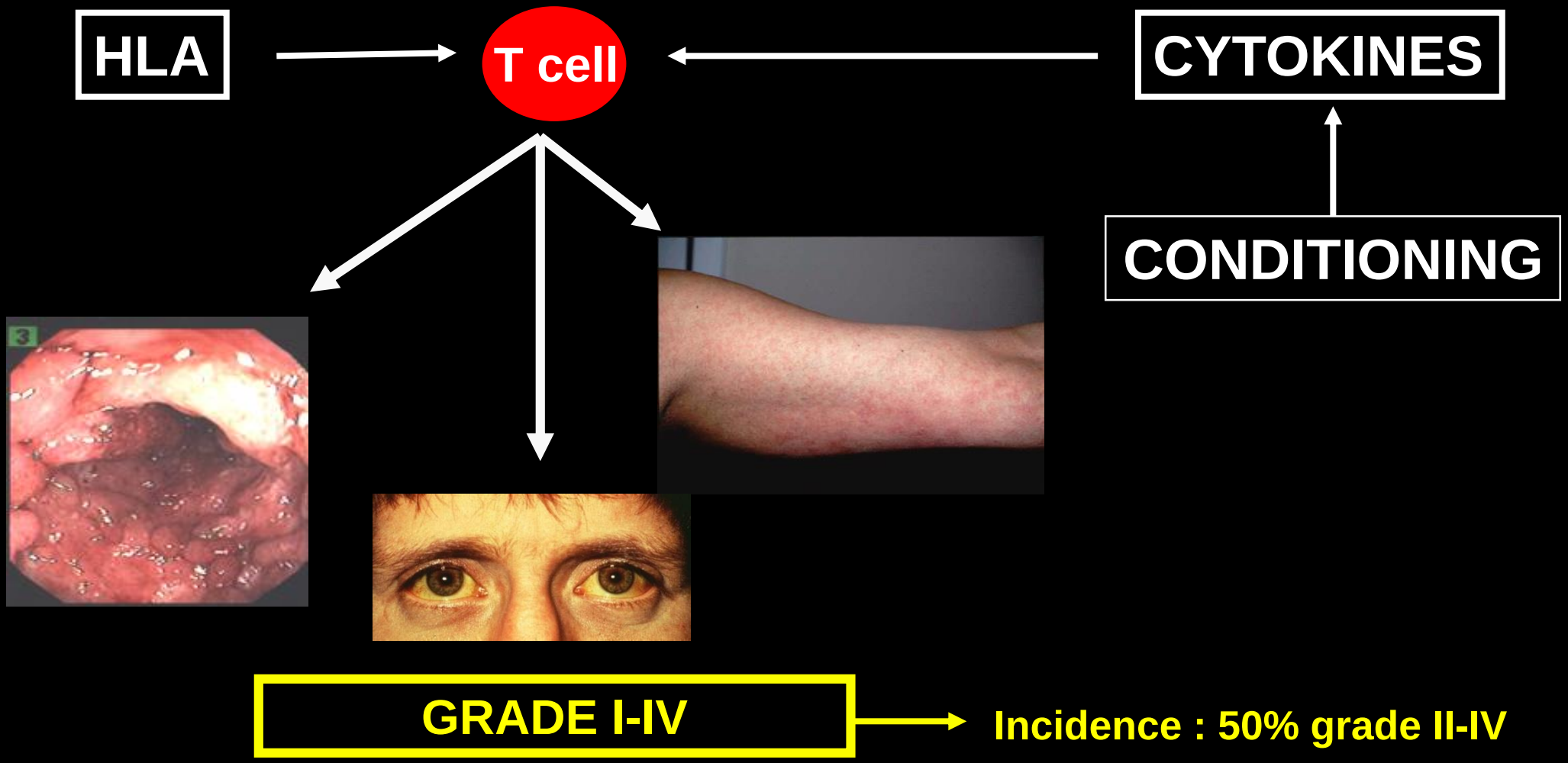
Carpenter & Greinix & Schoemans 2014

ACUTE GVHD

Clinical features

GVHD

Acute GVHD : before day 100



GVHD

Acute GVHD : risk factors

- **Donor**
  - HLA disparity (HLA, mHA)
  - Minor ABO mismatch
  - PBSC = marrow > CB
  - T cell dose
  - Sex : F → M
  - Age
  - Transfusions
  - Pregnancy
  - CMV positivity
- **Patient**
  - Type of prophylaxis
  - Intensity of conditioning
  - Gut anaerobic flora
  - Age
  - Leukemia
  - CMV positivity
  - Cytokine gene polymorphism

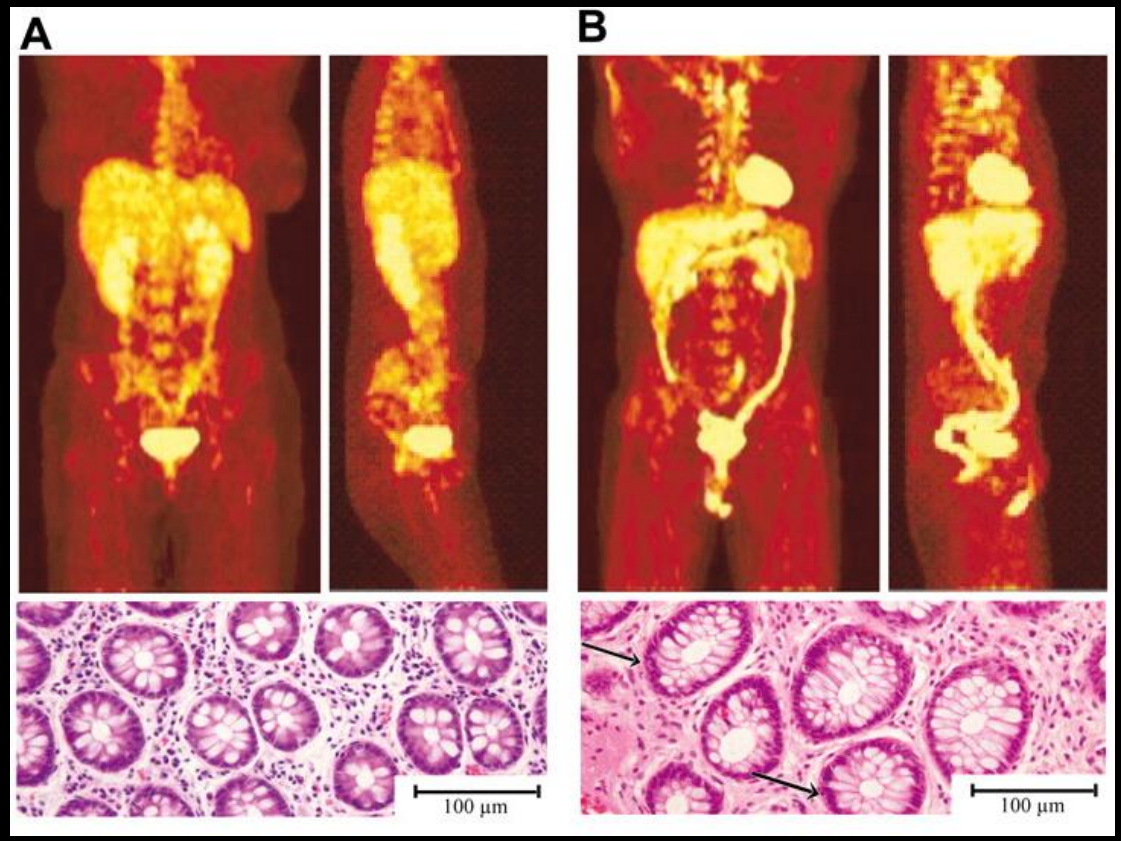
GVHD

Acute GVHD : Skin

GVHD

Acute GVHD : GI

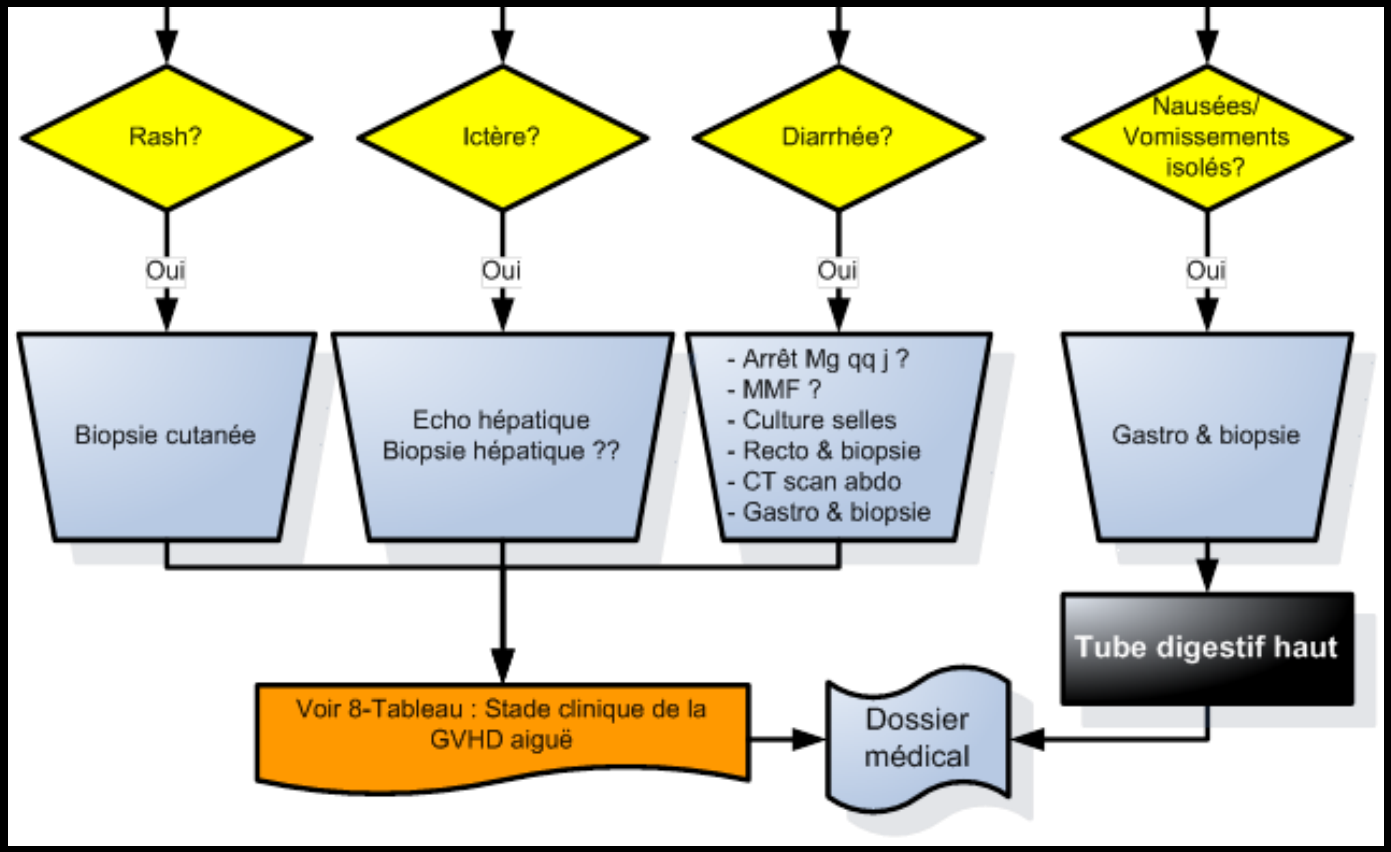
Diffuse small and large bowel wall thickening with a hyperattenuating mucosa (straight arrow) in the right lower quadrant. Associated dilated small bowel loops (curved arrow) and ascites (arrowhead) are seen in the left side of the pelvis.



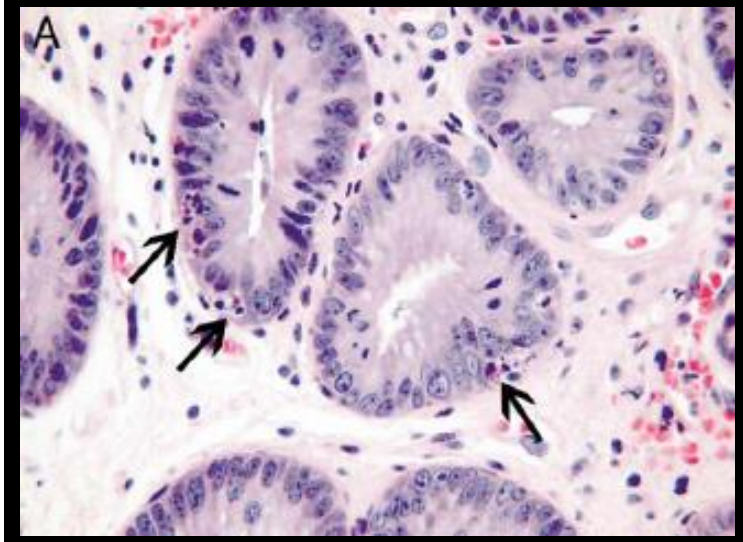
Stelljes et al. Blood 2008

GVHD

Acute GVHD : work-up



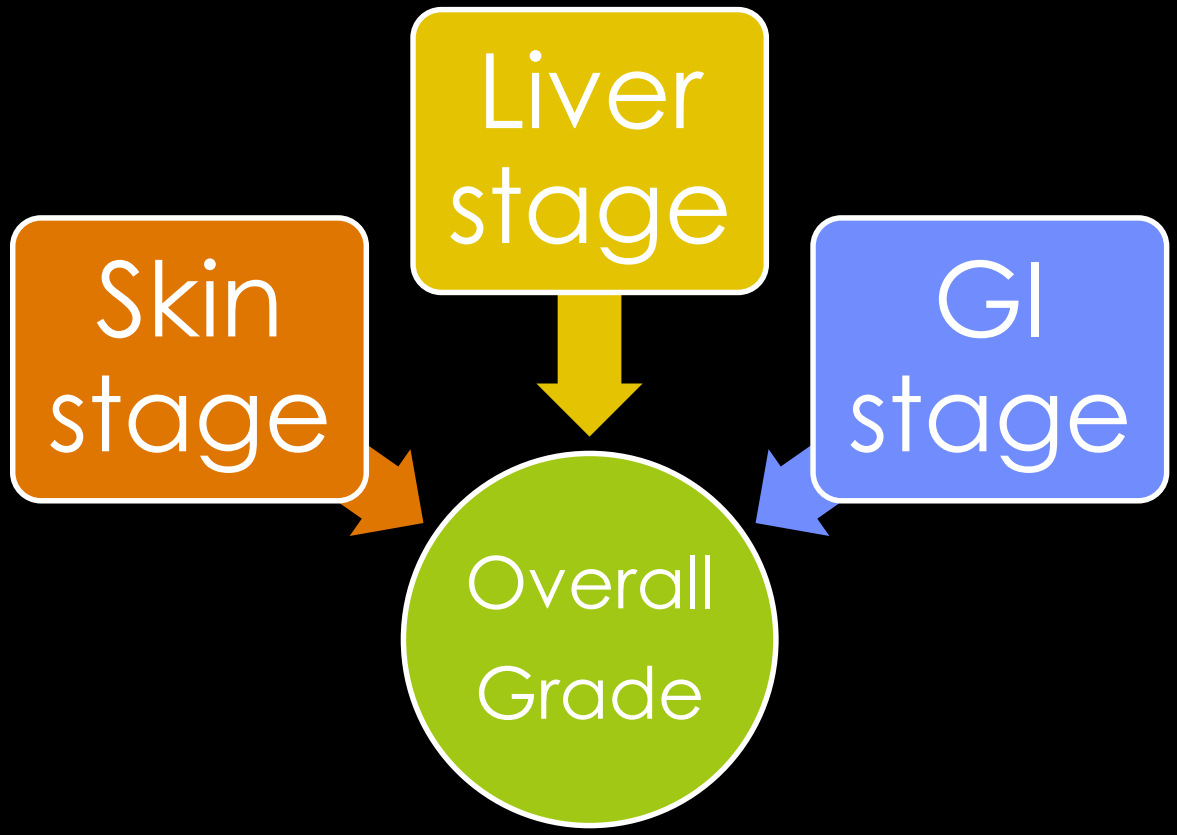
Acute GVHD
Apoptosis



Shulman et al, BBMT 12:31-47, 2006

GVHD

Acute GVHD : organ grading system



Carpenter & Greinix & Schoemans 2014

GVHD

Acute GVHD : organ grading system

Stage (organ)	Skin Maculopapular rash (% BSA)	Liver Bilirubin (mg/L)	Gut Diarrhea (ml/day)	Upper GI
1	< 25 %	20-30	500-1000	N / V Anorexia
2	25-50 %	30-60	1000-1500	
3	> 50 %	60-150	> 1500	
4	Erythrodermia ++ Bullae Desquamation ++	> 150	Pain +++ Ileus Bleeding ++	

1000 (1500) ml in adult = 15 (20) ml/kg in child

Glucksberg 1974

GVHD

AGVHD : Glucksberg grading system

Grade	Skin	Liver	Gut	Performance
1	1-2	0	0 *	Normal
2	0-3	1	1	Reduced
3	0-3	2-3	2-3	Much reduced
4	4	4	4	Bedridden

* Or isolated nausea / vomiting

Glucksberg 1974

GVHD

AGVHD : CIBMTR grading system

Grade	Skin	Liver	Gut	
A	1	0	0 *	
B	2	1-2	1-2	
C	3	3	3	
D	4	4	4	

* Or isolated nausea / vomiting

Rowlins, Br.J.Haematol., 1977

CHRONIC GVHD

Clinical features

GVHD

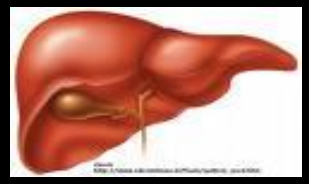
Chronic GVHD : after day 100

Allo-reactivity Auto-immunity

HLA → T cell + B cell

LIMITED

EXTENSIVE *30 %*



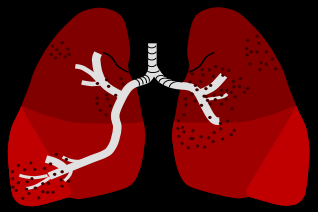
Liver

Skin

Other organs

Mucosa

GI tract



Lung

Eye

GVHD
Chronic GVHD : risk factors

- **Donor**
  - HLA disparity (HLA, mHA)
  - PBSC > marrow > CB
- **Patient**
  - Type of prophylaxis
  - Duration of prophylaxis (?)
  - Age
  - Latent herpes infection
  - Prior acute GVHD
  - Subclinical GVHD
  - Non-irradiated blood products

GVHD

Chronic GVHD : diagnostic criteria

Carpenter & Greinix & Schoemans 2014

GVHD

Chronic GVHD : signs & symptoms (1)

Table 1. *Signs and Symptoms of Chronic GVHD*

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)†		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseudomembranes† Ulcers†		Gingivitis Mucositis Erythema Pain

Filipovitch et al, BBMT 11:945-955, 2005

GVHD

Chronic GVHD : signs & symptoms (2)

Table 1. *Signs and Symptoms of Chronic GVHD*

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Eyes		New onset dry, gritty, or painful eyes‡ Cicatricial conjunctivitis Keratoconjunctivitis sicca‡ Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features Vaginal scarring or stenosis	Erosions† Fissures† Ulcers†		
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus†		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2 × upper limit of normal† ALT or AST >2 × upper limit of normal†
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology‡		BOOP
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis‡	Edema Muscle cramps Arthralgia or arthritis	

Filipovitch et al, BBMT 11:945-955, 2005

GVHD

Chronic GVHD : signs & symptoms (3)

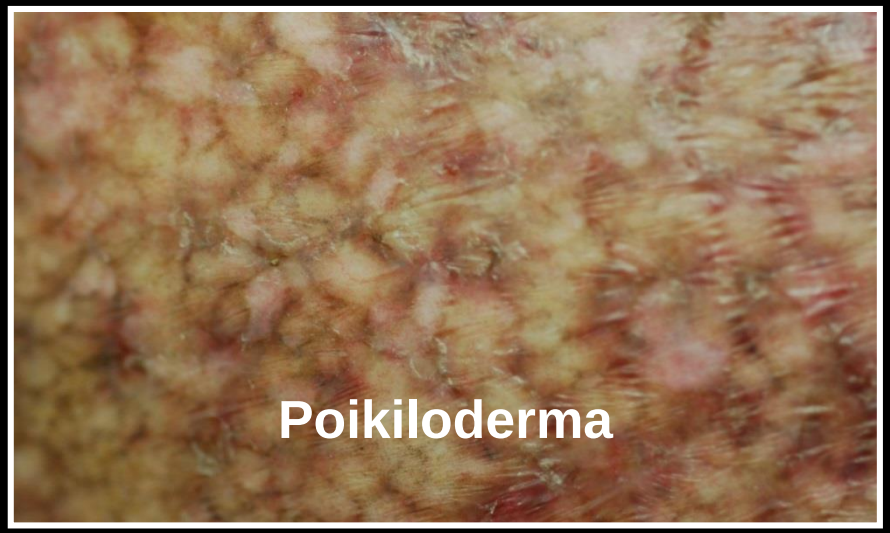
Table 1. *Signs and Symptoms of Chronic GVHD*

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

Filipovitch et al, BBMT 11:945-955, 2005

GVHD

Chronic GVHD : skin



GVHD

Chronic GVHD : skin

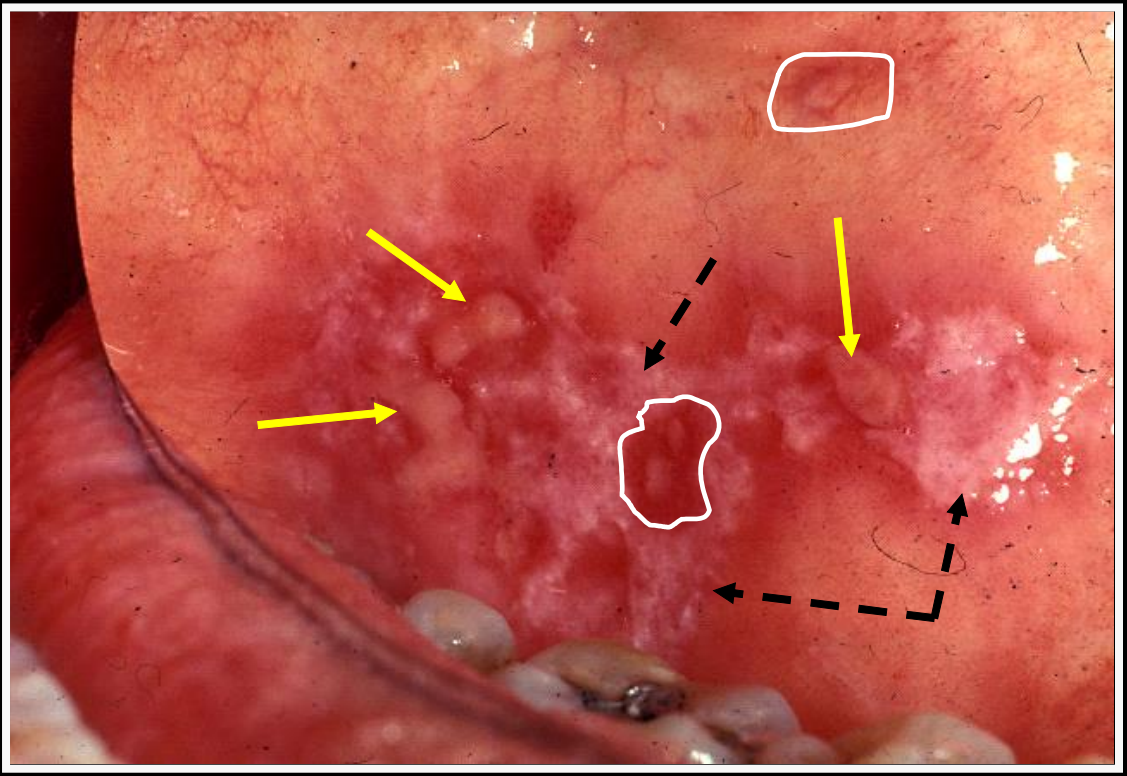
GVHD

Chronic GVHD : skin

Sclerotic chronic GVHD

GVHD

Chronic GVHD : mouth



Pseudomembranous ulcerations

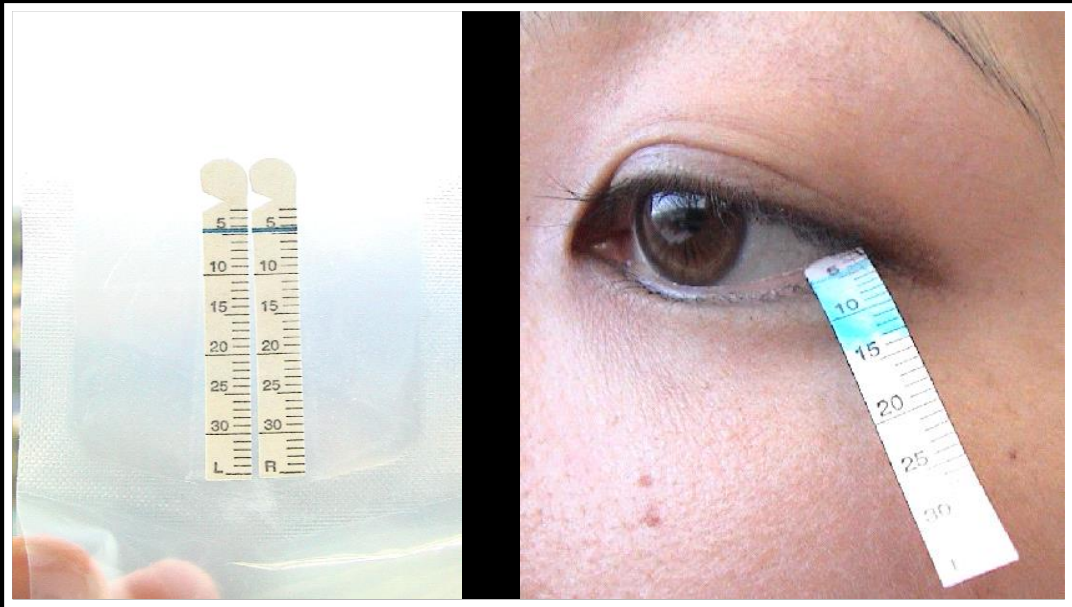
Pseudomembranous fibrin exudate

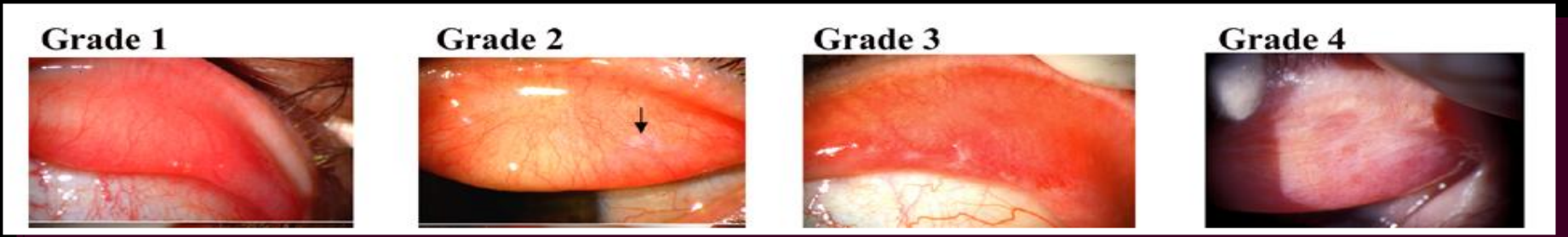
Severe lichenoid hyperkeratotic changes

Carpenter, Blood, 118:2679, 2011

GVHD

Chronic GVHD : eye



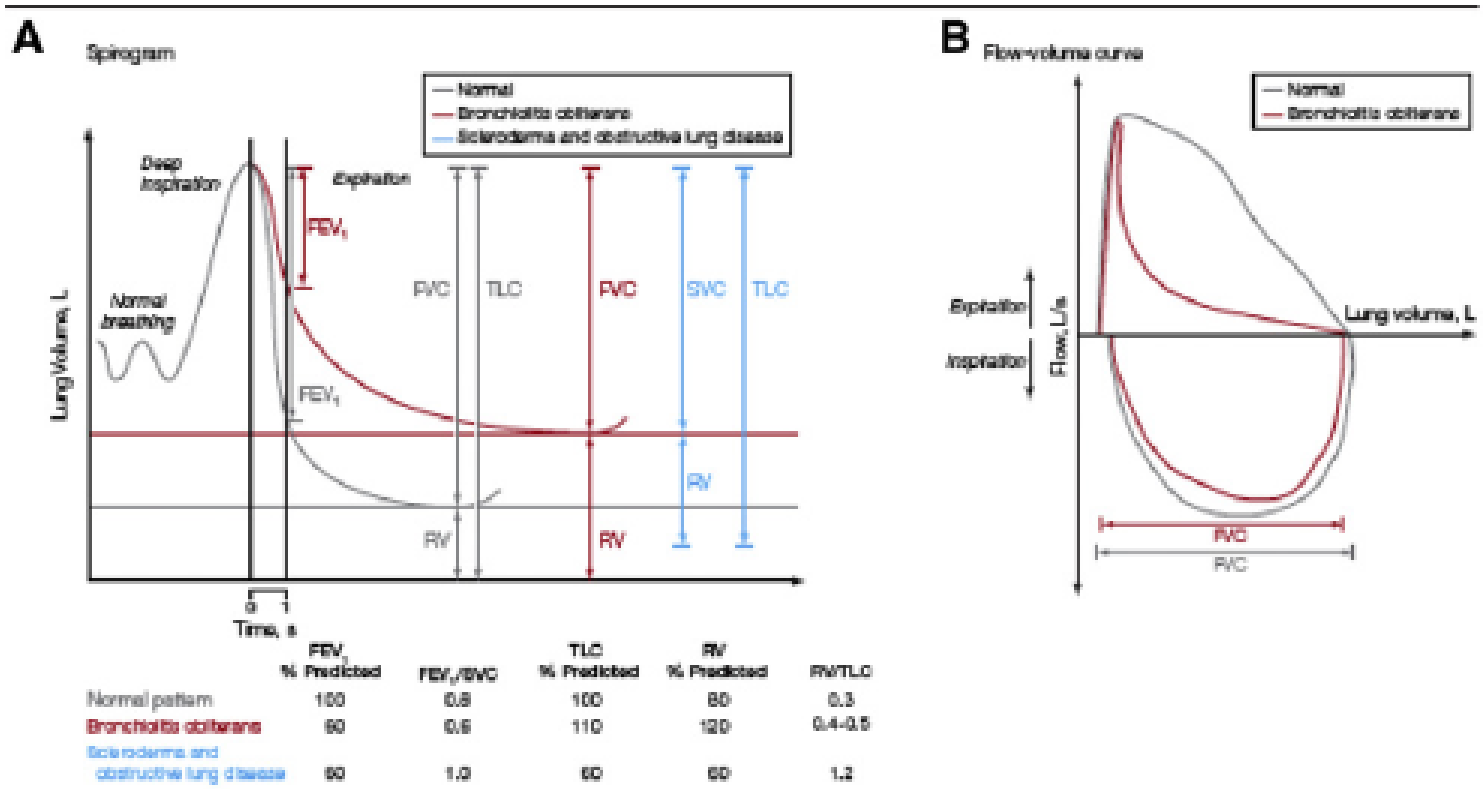


GVHD

Chronic GVHD : fasciitis

GVHD

Chronic GVHD : BO



	FEV1 % Predicted	FEV1/SVC	TLC % Predicted	RV % Predicted	RV/TLC
Normal pattern	100	0.8	100	80	0.3
Bronchiolitis obliterans	60	0.6	110	120	0.4-0.5
Scleroderma and obstructive lung disease	60	1.0	60	60	1.2

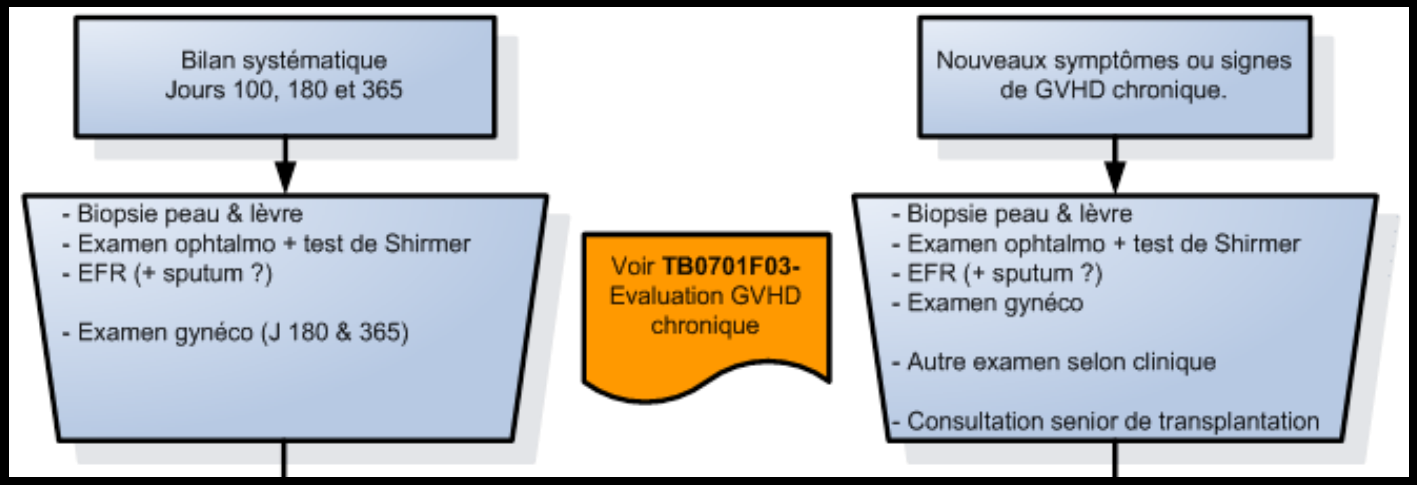
The pulmonary function test pattern shown for patients with scleroderma and obstructive lung disease has been observed in patients with sclerotic graft-vs-host disease. FEV_1 indicates forced expiratory volume in the first second of expiration; FVC, forced vital capacity; RV, residual volume; SVC, slow vital capacity; TLC, total lung capacity.

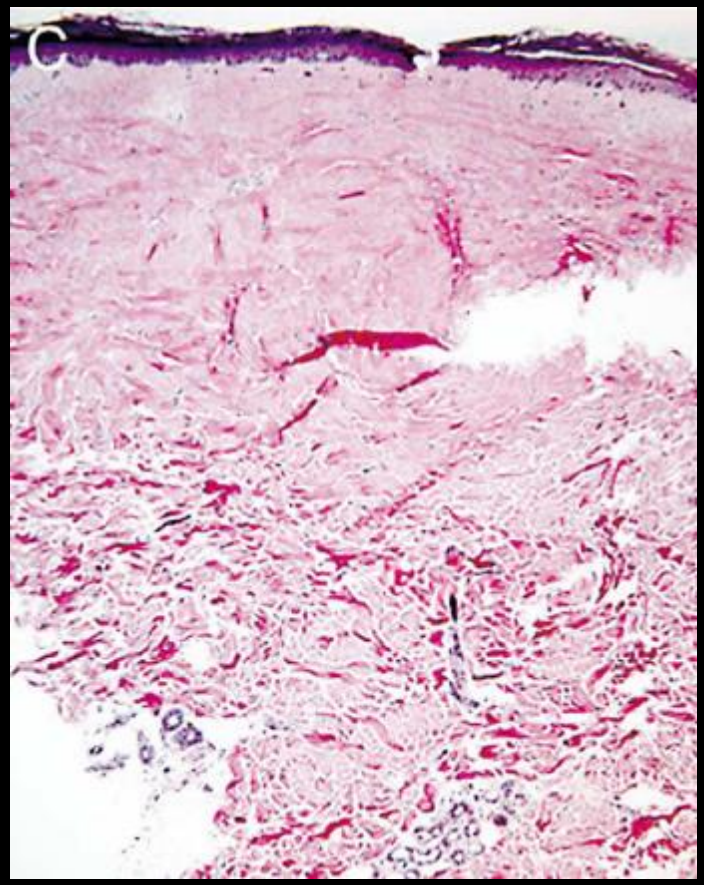
Figure 2. Diagram of spirogram and flow volume curves representative of patients with bronchiolitis obliterans syndrome [70].

Chien and al, BBMT, 16:S106, 2010

GVHD

Chronic GVHD : work-up





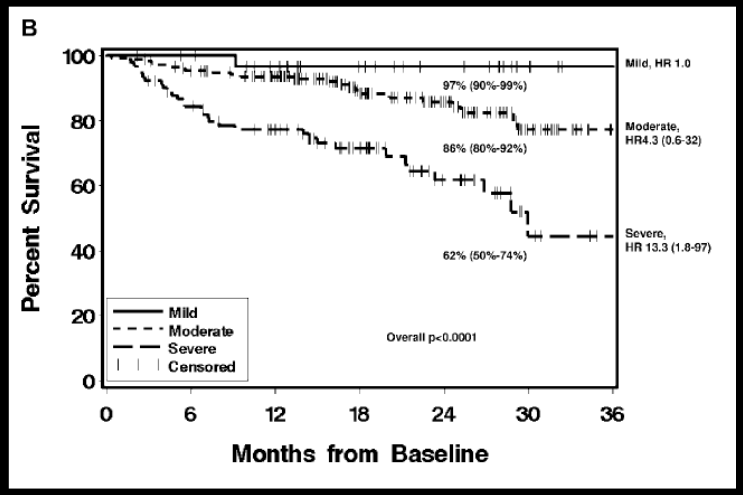
Chronic GVHD
Sclerosis

Shulman et al, BBMT 12:31-47, 2006

GVHD
Chronic GVHD : grading

- **Classical grading system**
  - Subclinical (positive biopsy or Shirmer without symptoms)
  - Limited
  - Extensive
- **NIH consensus grading system**
  - Mild (almost no complain but clinically apparent)
  - Moderate
  - Severe (life-threatening or severe disability)

Severity	Mild	Moderate	Severe
Number of involved organs	1-2	≥3	≥3
Severity of organ manifestations	1 (excluding lung)	2 (or lung 1)	3 (or lung 2)



Wolff et al, BBMT 16:1611-1628, 2010

Arai et al, Blood, 118:4242, 2011

GVHD

Chronic GVHD : organ grading

Eight organs : skin, mouth, eyes, GI, liver, lung, genitalia and muscles

- **Score 0** — No problem
- **Score 1** — Minor symptoms without impact
- **Score 2** — Symptoms impacting activities of daily life
- **Score 3** — Symptoms resulting in disability

Carpenter & Greinix & Schoemans 2014

GVHD

Chronic GVHD : global grading

# OF ORGANS	MILD	MODERATE	SEVERE
1	Score 1	Score 2	Score 3
2	Score 1	Score 2	Score 3
3		Score 1	Score 3
Lung		Score 1	Score 2

MILD = 1 or 2 organs (but not lung) with maximum Score 1

MODERATE = Lung Score 1 <u>or</u> ≥ 3 organs at Score 1 <u>or</u> at least 1 organ at Score 2

SEVERE = Lung Score 2 <u>or</u> Score 3 in any organ

Carpenter & Greinix & Schoemans 2014

GVHD

Chronic GVHD : NIH grading (1)

	Score 0	Score 1	Score 2	Score 3
Performance score: ☐ KPS ECOG LPS	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
Skin Clinical features: ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritis ☐ Hair involvement ☐ Nail involvement ☐ **% BSA involved**	☐ No symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA OR deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritis
Mouth	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
Eyes **Mean tear test(mm):** ☐ >10 ☐ 6-10 ☐ ≤10 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops >3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affectind ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI tract	☐ No symptoms	☐ Symptoms such as dysphagia, nausea, vomiting, abdominal pain or diarrhoea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** oesophageal dilation
Liver	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dL or Bilirubin enzymes 2-5 x ULN	☐ Bilirubin or enzymes >5 x ULN

Filipovitch et al, BBMT 11:945-955, 2005

GVHD

Chronic GVHD : NIH grading (2)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS†	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
FEV1 ☐ DLCO ☐	☐ FEV1 > 80% **OR** LFS=2	☐ FEV1 60-79% **OR** LFS 3-5	☐ FEV1 40-59% **OR** LFS 6-9	☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact where applicable (none – 0,mild -1, moderate -2, severe – 3)

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl ___	Progressive onset___	

Filipovitch et al, BBMT 11:945-955, 2005

GVHD

Prevention

GVHD
Prevention of GVHD : T-cell depletion

- **Various methods**
  - HSC selection (CD34, AC133)
  - T cell removal (elutriation, McAb …)
  - Selective depletion (CD8, CD6 …)
  - Campath-1 (in the bag, in vivo)
  - ATG (in vivo)
  - Alloreactive depletion
- **Full T-cell depletion = most effective prevention**
- **Increased risk of relapse**

GVHD
Prevention of GVHD : drugs

- Old standard = MTX
- Current standard = ciclosporine ± MTX
  Alternative = tacrolimus ± MTX
- Others (in association with calcineurin inhibitor)
  - Corticosteroids (CB)
  - ATG (mismatch, PBSC, MUD, CB) — 15 mg/kg x 3 (ATG Fresenius®)
    2.5 mg/kg x 3 (Thymoglobuline®)
  - MMF (minitransplant) — 30-45 mg/kg/d
  - Sirolimus — 2 mg/d

GVHD

Prevention of GVHD : CSP or TAC

- CSP IV 4 mg/kg (CIV or 12-h infusion or 2 doses)
  PO 6 mg/kg (in 2 doses)

Trough levels	100-150 ng/ml	Very low risk (TCD)
	150-250 ng/ml	Low risk (marrow)
	250-400 ng/ml	High risk (PBSC, CB)

- TAC IV 0.04 mg/kg (CIV or 12-h infusion or 2 doses)
  PO 0.06 mg/kg (in 2 doses)

Trough levels	4- 6 ng/ml	Very low risk (TCD)
	5-10 ng/ml	Low risk (marrow)
	10-15 ng/ml	High risk (PBSC, CB)

Side effects : similar but diabetes (tacro) vs HTA (ciclo > tacro)

GVHD
Prevention of GVHD : MTX

- MTX : IV 15 mg/m2 (day 1), 10 mg/m2 (days 3, 6, 11)

- Dose reductions

Creatinin	Dose	Bilirubine	Dose	Mucositis (Seattle)	Dose
< 15	100 %	< 20	100 %	0	100 %
15-17	75 %	20-30	50 %	1	100 %
18-20	50 %	31-50	25 %	2	50-100 %
> 20	0	> 50	0	3	0

GVHD

Prevention of GVHD : ATG

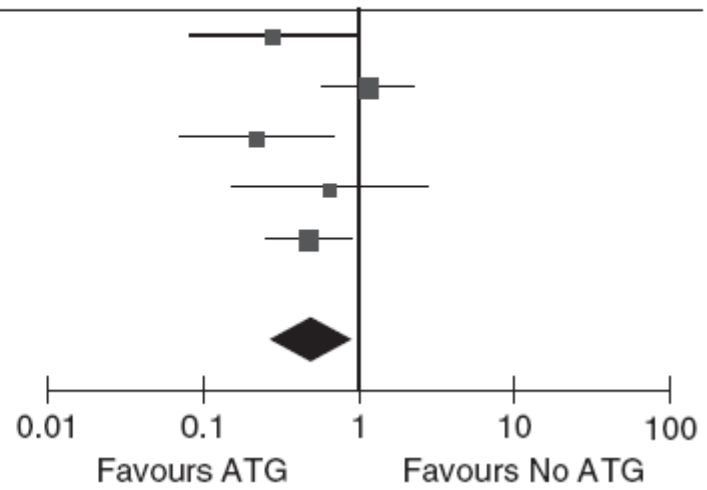
Grade 3-4 AGVHD

a Acute GVHD III/IV

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Bacigalupo 2001 A	-1.27481	0.617802	15.7%	0.28 [0.08, 0.94]
Bacigalupo 2001 B	0.139262	0.346355	26.9%	1.15 [0.58, 2.27]
Bacigalupo 2010	-1.50408	0.576204	17.0%	0.22 [0.07, 0.69]
Champlin 2007	-0.42744	0.743084	12.3%	0.65 [0.15, 2.80]
Finke 2009	-0.74291	0.324172	28.1%	0.48 [0.25, 0.90]
Total (95% CI)			**100.0%**	**0.51 [0.27, 0.94]**

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 8.44$, df = 4 (P = 0.08); $I^2 = 53\%$

Test for overall effect: Z = 2.17 (P = 0.03)



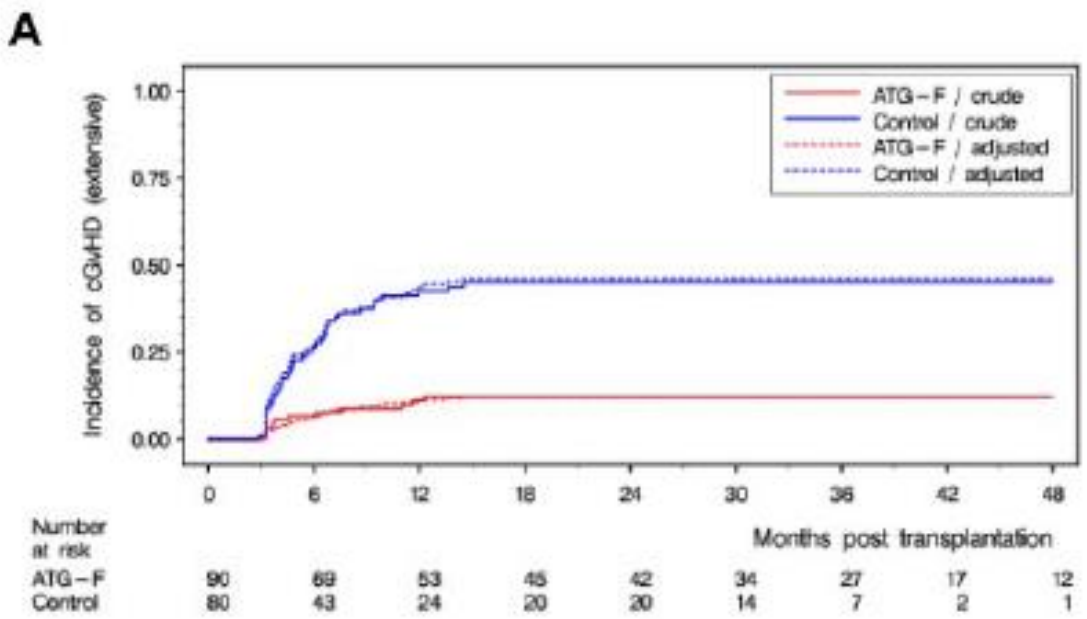
No significant difference for grade 1 or grade 2

Metaanalysis of 7 randomized trials in 733 patients (any donor, any SC source, any conditioning, any ATG)

Kumar et al, Leukemia 26:582–588, 2012

GVHD

Prevention of GVHD : ATG



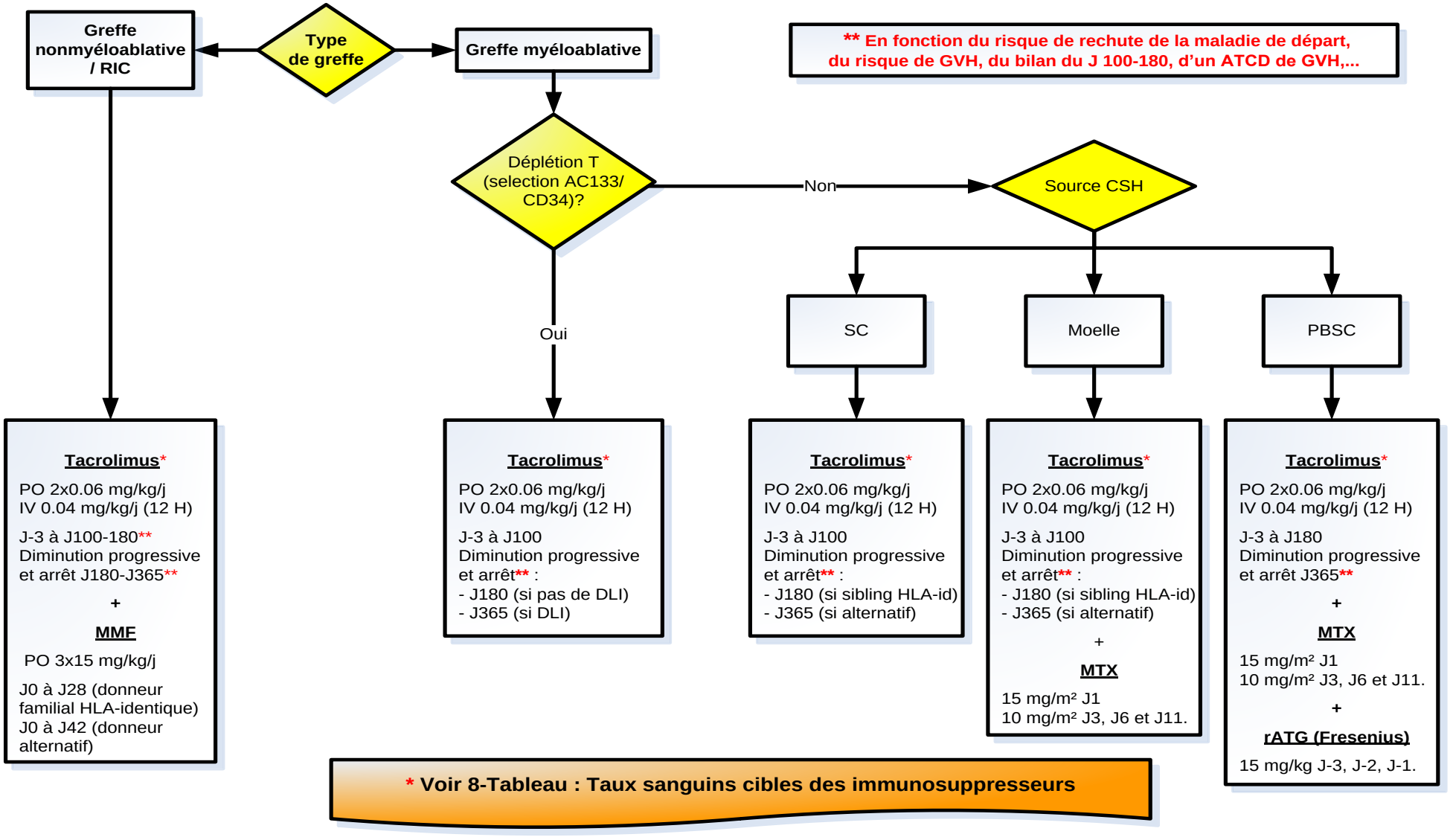
Extensive chronic GVHD
3-year CI, 12.2% to 45.0%; HR =0.20, 95% CI, 0.10 to 0.39, $P < .0001$

MUD transplant, randomization with or without ATG (Fresenius) = Finke trial

Socié et al, Blood, 117:6375, 2011

GVHD

Prevention of GVHD : algorythm



GVHD

Treatment

GVHD

Treatment of acute versus chronic GVHD

- **Acute GVHD**
  - Corticosteroids
  - ATG
  - Sirolimus
  - MMF
  - Cyclophosphamide
  - Pentostatine
  - PUVA (skin)
  - Photopheresis
  - Monoclonal Ab
  - MSC

- **Chronic GVHD**
  - Corticosteroids
  - CSP, tacrolimus
  - Sirolimus, everolimus
  - Azathioprine, MMF
  - Cyclophosphamide
  - Pentostatine
  - PUVA (non-sclerodermic skin)
  - Photopheresis
  - Thalidomide
  - Imatinib
  - Hydroxychloroquine, acitrétine
  - TLI (1 Gy)

ACUTE GVHD

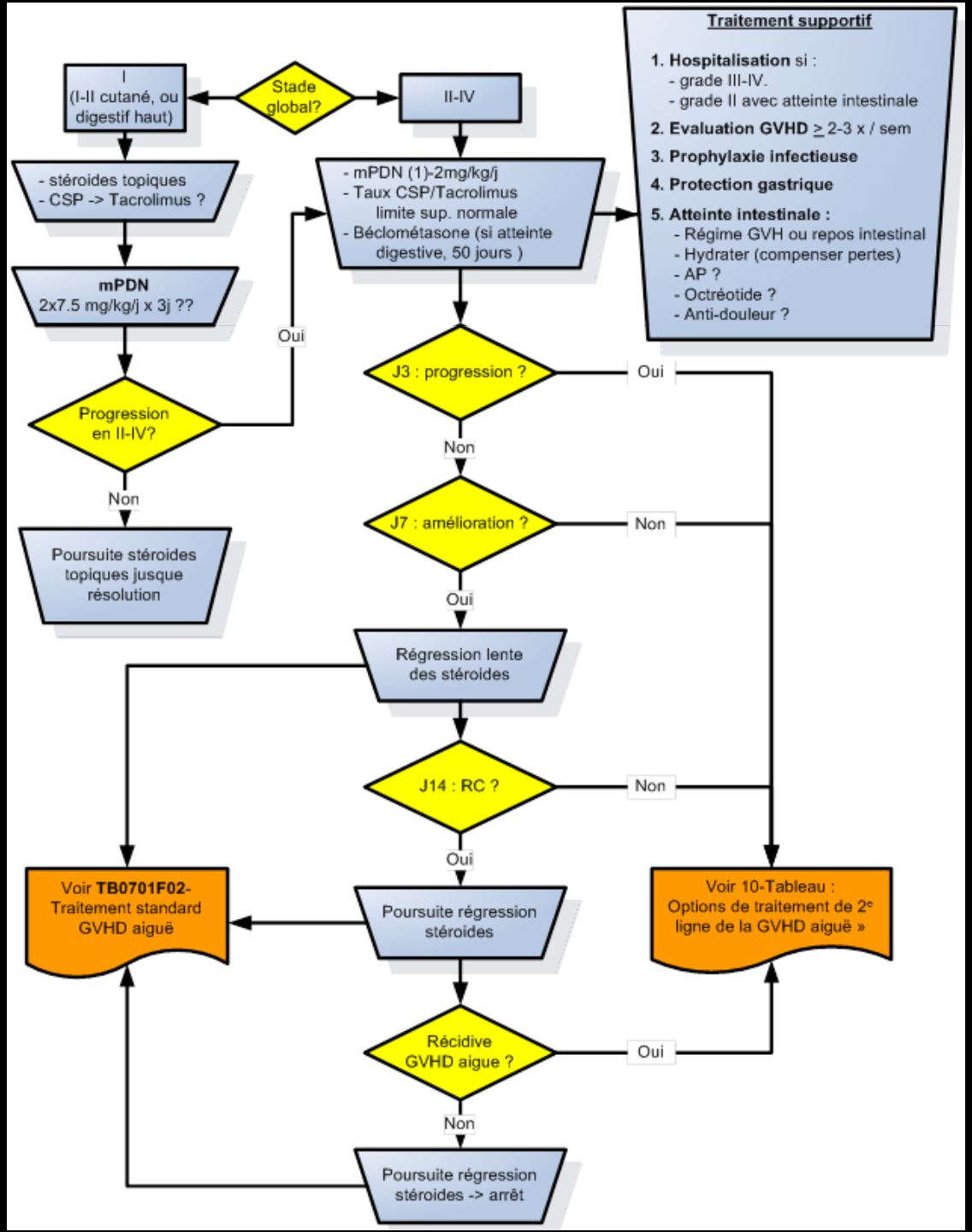
Treatment

GVHD
Treatment of acute GVHD

- **Standard = corticosteroids**
  - Standard dose = 1-2 mg/kg for 1-2 wks
    slow taper over 3 months
  - High dose = 5-20 mg/kg for 3 days
    1) Grade II skin GVHD : stop
    2) Grade IV/resistant GVHD : continue with standard regimen
- **Alternatives for resistant GVHD**
  - ATG : 30 mg/kg/d x 3-5 days or 15 mg/kg/d days 1-3-5-7-9-11
  - McAb
  - PUVA (skin GVHD)
  - Photopheresis
  - MSC
  - Sirolimus, cyclophosphamide, pentostatin, MMF, MTX …

GVHD

Treatment of acute GVHD



CHRONIC GVHD

Treatment

GVHD
Treatment of chronic GVHD

- Standard = cyclosporine + mPDN
- Alternative = tacrolimus + mPDN (more effective ?)
- Others drugs
  - Thalidomide 200-600 mg/d
  - Azathioprine 1.5 mg/kg/d
  - MMF 30 mg/kg/d
  - Sirolimus 1-2 mg/d (dosage !)
  - Everolimus 1-2 mg/d (dosage !)
- Physical methods
  - PUVA
  - Photopheresis
  - Low dose TLI (1Gy)

GVHD

Treatment of cGVHD : CSP + mPDN

Week	mPDN (mg/kg)		CSP (mg/kg)	
	Day A	Day B	Day A	Day B
1	1	1	6	6
2		1	0	6
3		0.50		
4		0.25		
5		0.125		
6		0.06		
7		0		
20	1			
21	0.75			
22	0.50			
40	0.50			6

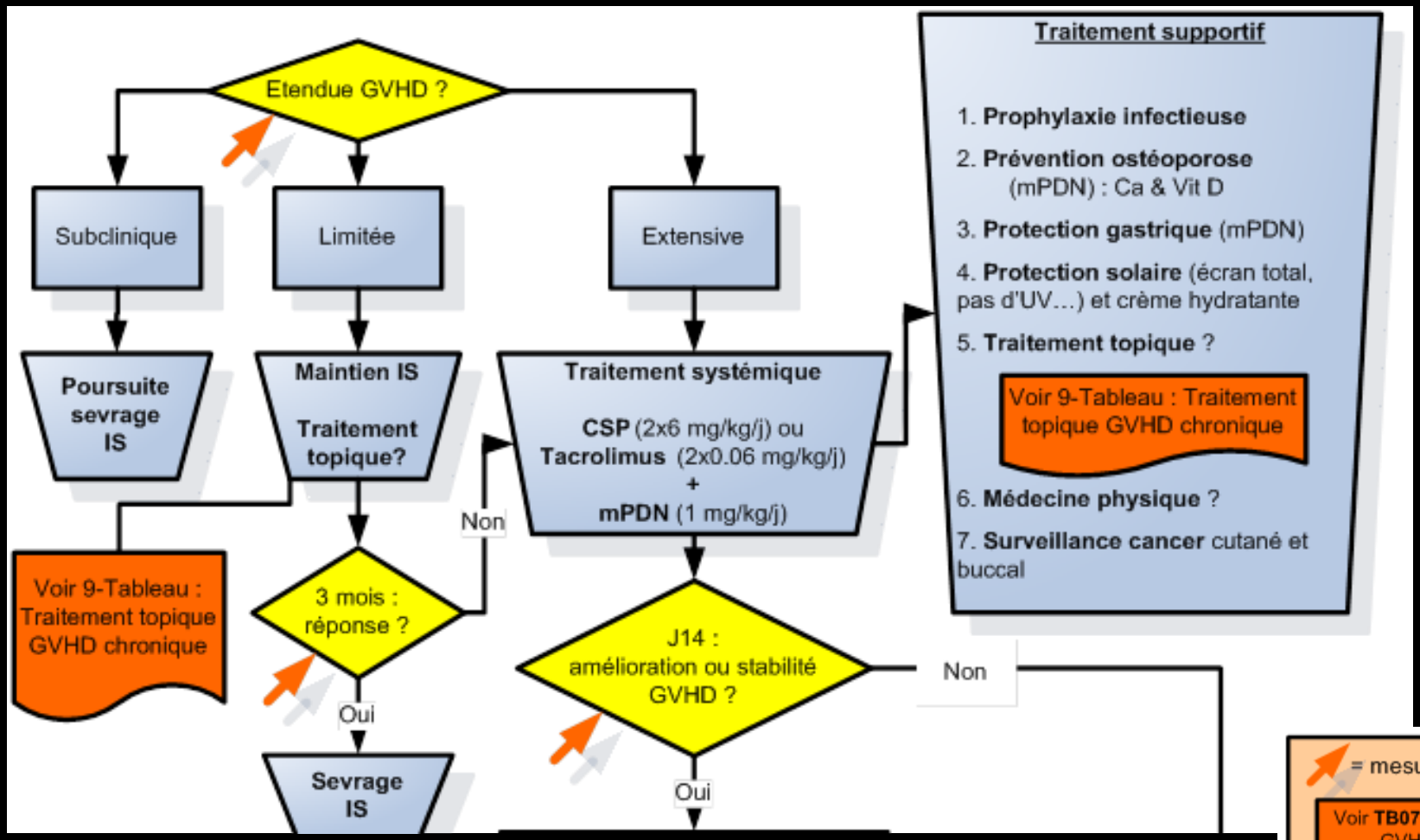
GVHD

Treatment of cGVHD : CSP + mPDN

Week	mPDN (mg/kg)		CSP (mg/kg)	
	Day A	Day B	Day A	Day B
40	0.50			6
41	0.25			↓
42	0.125			
43	0.06			
44	0			6
45				5
46				4
47				3
48				2
49				1
50				0

GVHD

Treatment of chronic GVHD (1)

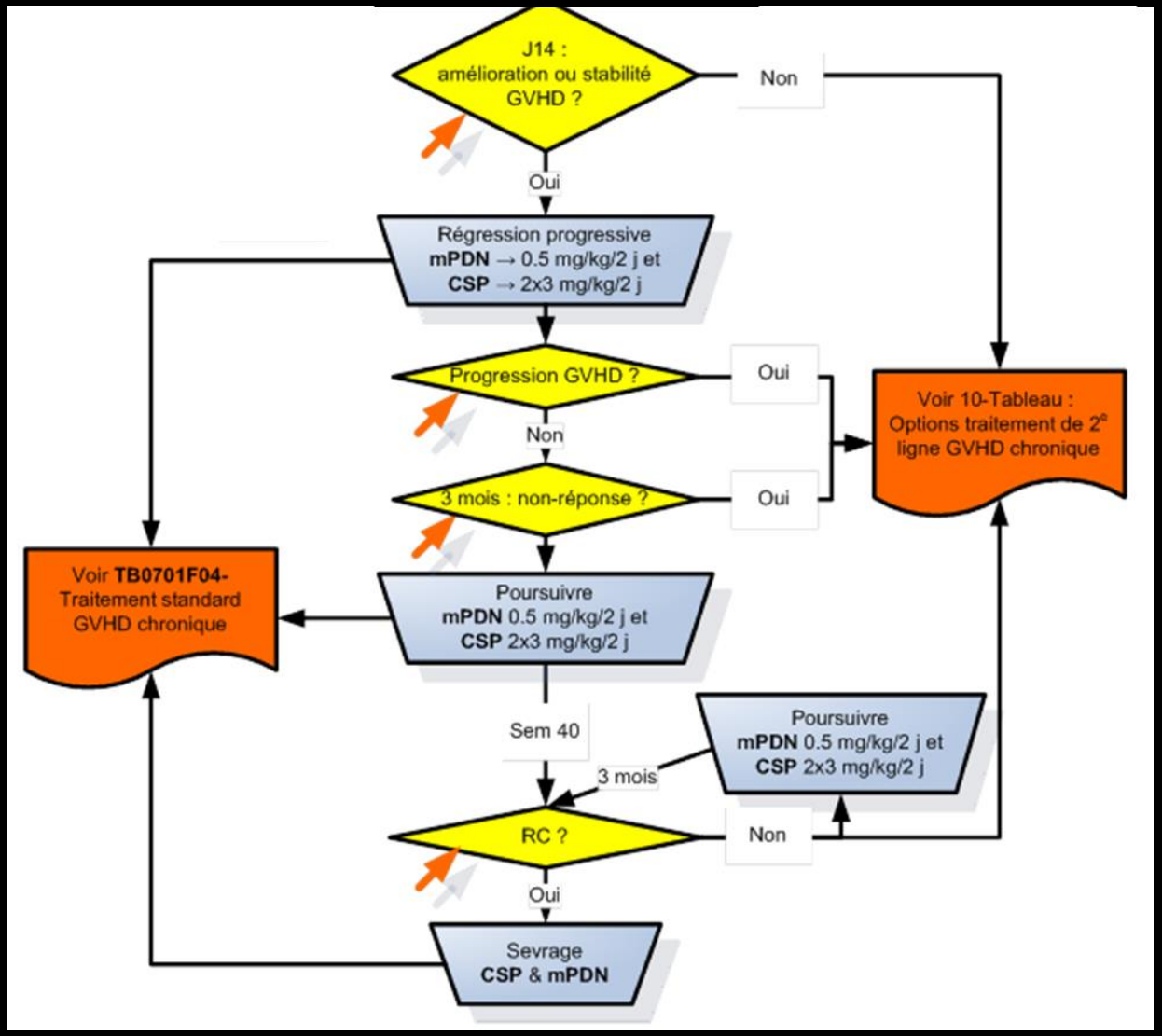


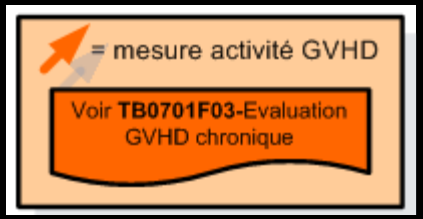
= mesure activité GVHD

Voir TB0701F03-Evaluation GVHD chronique

GVHD

Treatment of chronic GVHD (2)





CHRONIC GVHD

Treatment : first line

Agent	Recommendation (citation number of references)	Evidence	Side Effects	Comments
Steroids	A [16-18]	I	Osteoporosis, avascular necrosis of the bone, diabetes	Important but need to spare steroids because of side effect profile, generally sufficient in primary treatment of mild cGVHD as single agent, may be used in combination with CNI in moderate or severe cGVHD
CNI	C [16,17]	II	Renal toxicity, hypertension	Only be used in combination with steroids, spares steroids, lower rate of avascular necrosis of the bone, may be considered in combination with steroids in primary treatment of severe cGVHD as well as in CNI dependent moderate cGVHD
~~MMF in triple agent combinations~~	D [19]	II	GI complaints, infectious and relapse risk	Failure to improve efficacy in a randomized trial documented
~~Azathioprine~~	D [18]	II	Hematologic toxicity, infectious risk	Adverse outcome in a randomized trial in combination with steroids
~~Thalidomide~~	D [20,21]	II	Neurotoxicity, sedation, constipation, thrombosis	May be used in concomitant relapse of multiple myeloma

Wolff et al, BBMT 16:1611-1628, 2010

CHRONIC GVHD

Treatment : second line

Agent	Recommendation	Evidence	Side Effects	Comments
Steroids	B	III-1	osteoporosis, avascular necrosis, diabetes	important but need to spare steroids because of side effect profile
Photopheresis	C-1	II	venous access required	spares steroids, excellent safety profile
mTOR inhibitors	C-1	III-1	TAM, hyperlipidemia, hematotoxicity	increased risk for TAM in combination with CNI, lower efficacy in thrombocytopenia, requires frequent monitoring
CNI	C-1	III-1	renal toxicity, hypertension	spares steroids, should be avoided in renal impairment
MMF	C-1	III-1	GI complaints, infectious and relapse risk	increased risk for viral reactivation, spares steroids, GI toxicity may mimic GVHD clinically and histologically
Pentostatin	C-2	II	Hematotoxicity, infectious risk	best results in children, caution in presence of impaired marrow function, long-term immunosuppression
MTX	C-2	III-1	Hematotoxicity	best response in mucocutaeous cGVHD, spares steroids
Imatinib	C-2	III-1	Fluid retention	best results in sclerotic skin lesions, potentially effective in mild and moderate BO
Rituximab	C-2	II	Infectious risk	effective in auto-antibody mediated manifestations as well as cutaneous and musculosceletal cGVHD
Hydroxychloroquine	C-2	III-2	GI complaints	best results in mucocutaneous and liver involvement
Clofazimine	C-2	III-2	GI complaints, skin hyperpigmentation	best results in mucocutaneous cGVHD
Thoracoabdominal irradiation	C-2	III-2	Hematotoxicity	best results in fasciitis or steroid dependent mucocutaneous cGVHD, caution in presence of impaired marrow function
Pulse of steroids	C-2	III-2	Infectious risk	rapid control of symptoms, identification of steroid resistance
Thalidomide	C-3	II	Neurotoxicity, sedation, constipation	may be used in concomitant relapse of MM
Azathioprine	C-3	III-1	Hematotoxicity, infectious risk	increased risk for oral malignancies
Retinoids	C-3	III-2	Skin toxicity, Hyperlipidemia	effective in sclerotic skin lesions
Alemtuzumab	C-4	III-3	Infectious risk	last resort
Alefacept	C-4	III-3	Infectious risk	last resort
Etanercept	C-4	III-3	Infectious risk	may be used in overlap syndrome with GI manifestations

Wolff et al, BBMT 17:1-17, 2011

CHRONIC GVHD

Treatment : topical

Organ	Agent (citation number of references)	Recommendation	Evidence	Side Effects	Comments
Skin	Topical steroids [7]	C-1	III-1	Skin atrophy	Neck down: mid-strength steroids if no response upper strength steroids, face: hydrocortisone 1%
	Tacrolimus/Pimecrolimus [22-25]	C-1	III-1	Long-term risk for cutaneous malignancies	Should be given twice daily
	PUVA [26-31]	C-1	III-1	Phototoxicity, risk for cutaneous malignancies	Should not be used with phototoxic medication
	UVA [32-35]	C-1	III-1	Phototoxicity, risk for cutaneous malignancies	Requires no UV protection after treatment, should not be used with phototoxic medication
	UVB [36]	C-1	III-2	Phototoxicity, risk for cutaneous malignancies	Only effective in lichenoid cGVHD
GI	Topical steroids [37-39]	C-1	III-1		Either budesonide or beclomethasone
Lung	Topical steroids	B	III-2		May be combined with betamimetic agents
Oral	Topical steroids [40-44]	C-1	III-1-III-3	Best results with topical budesonide	Requires oral hygiene and possibly topical antifungals
	Topical tacrolimus /cyclosporine [45-51]	C-2	III-1	Burning	Potentially increases risk for oral malignancies, may be combined with topical steroids
	Topical PUVA/UVB [44,52-54]	C-2	III-1	Optional treatment option for refractory manifestations	Psoralene may be given topically or systemically
Eye	Topical steroids [55,56]	C-1	III-1	Risk for corneal thinning and infectious keratitis	Duration of exposure should be limited
	Topical cyclosporine [57-60]	C-1	III-1	Burning, stinging	Fewer long-term side effects compared to steroids, high long-term efficacy
Vaginal	Topical steroids [61-64]	B	III-3	Increased risk for infectious complications and atrophy	Topical estrogen application and antifungal prophylaxis suggested
	Topical tacrolimus/ cyclosporine/pimecrolimus [63-65]	B	III-3	Burning	Less well tolerated but better long-term efficacy

Wolff et al, BBMT 16:1611-1628, 2010

GVHD

Chronic GVHD : IS and survival

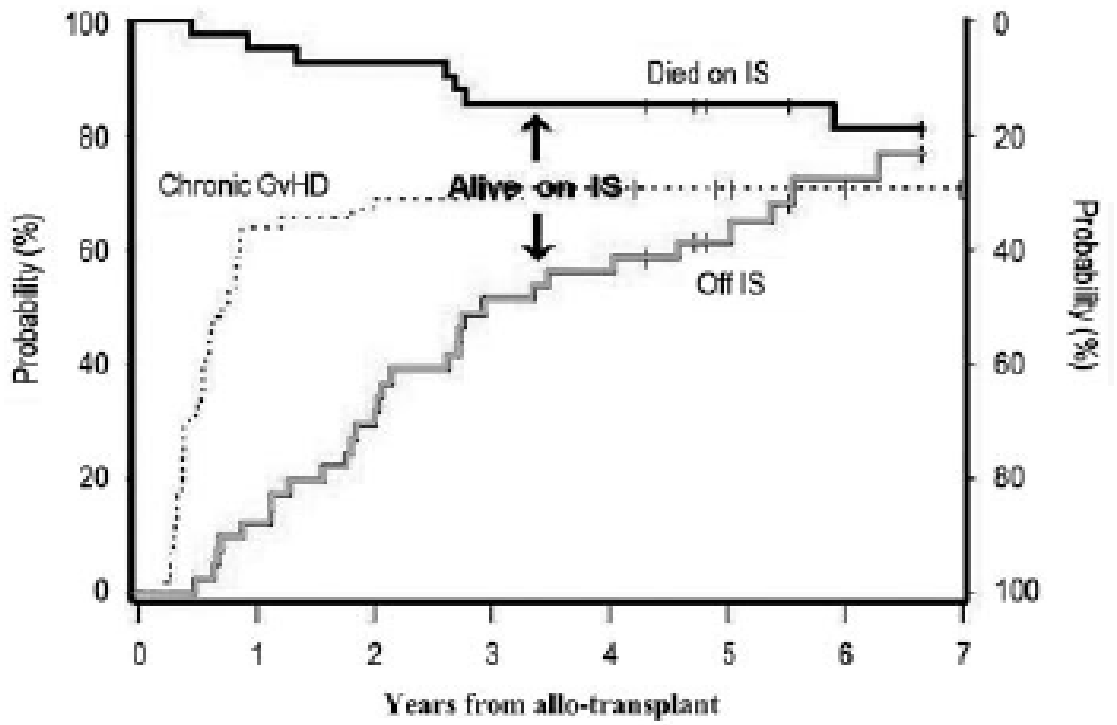


Figure 4. Probability of being alive on or off immunosuppression (IS) medications among patients who developed limited or extensive chronic GVHD. Overall incidence of chronic GVHD (dotted line); patients who died while on IS medications (black solid line); and patients alive who discontinued all IS medications (gray solid line) after developing chronic GVHD. The distance between the black and solid lines represents patients who are alive and still on IS medications (see also "Long-term immunosuppression").

Giaccone et al, Blood, 117:6721, 2011

CHRONIC GVHD

Supportive care

GVHD

Treatment of cGVHD : infection prophylaxis

- **Pneumococcus :** Penicillin
- **CMV :** preemptive Ganciclovir
- **Pneumocystis :** Bactrim, dapsone, aerolized Pentamidine
- **Mycoses :** Posaconazole

- IV Ig if low IgG levels
- Endocarditis prophylaxis if dental or invasive procedures
- Vaccinations : pneumococcus, H influenzae

GVHD

Treatment of chronic GVHD : supportive care

- **Skin**
  - Skin protection (hats, sunscreen, no UV …)
  - Anti-histaminic drugs
  - Topical CS (bid) * Face : hydrocortisone (Cremicort®)
    * Body : Locoïd® → Diprosone® → Dermovate®
  - Topical tacrolimus (bid) : Protopic® 0.03% or 0.1% bid
  - Lubrication cream
  - Physical therapy (joints)
- **Lung**
  - Bronchodilators : Duovent®…
  - Steroids (2-4 x/d) : Pulmicort®, Flixotide®…
  - Azythromycine 500 mg/d x 3 d, then 250 mg TIW
  - Montelukast (10 mg/d) : Singulair®, Montelukast®
  - O_2
  - Pulmonary rehabilitation

GVHD

Treatment of chronic GVHD : supportive care

- **Mucosa**
  - **Dexamethasone mouth wash : 10 min, 4 x/day**
    - ***Nystatine 2 millions U***
    - ***Lidocaïne Hcl 250-(500) mg*** **(do not swallow !)**
    - ***Dexamethasone 30 mg***
    - ***Glycerin 10 ml***
    - ***Propyleneglycol 10 m*****l**
    - ***Klucel 2 gr***
    - ***Conserving water ad 300 ml***
  - **Budesomide mouth wash : 10 min, 3 x/d, 1 (Entocort® or Budenofalk®) in 5 ml**
  - **Ciclosporine mouth wash : 10 min, 4 x/d, 5 ml Neoral Sandimmun®**
  - **Lips : Diprosone®**
  - **Pain : Lidocaine spray or pellets**
  - **Dental follow-up**
  - **Saliva substitutes (Xerotin®), stimulants, pilocarpine**

GVHD

Treatment of chronic GVHD : supportive care

- **Gut**
  - Beclomethasone diproprionate 4 x 1 mg/day
    - Upper GI tract : normal tablets
    - Lower GI tract : enteric coated tablets
  - Higher dose steroids
    - Lower GI tract :
      Beclomethasone diproprionate (Clipper®) 5 mg/d enteric coated tablets
      Budesonide (Entocort®, Budenofalk®) 3 mg 3 x/d enteric coated tablets
  - Pancreatic enzyme replacement
  - Gastric protection : proton pump inhibitors
- **Liver**
  - Acide ursodesoxycholic (Ursofalk®)

GVHD

Treatment of chronic GVHD : supportive care

- **Vulva / vagina**
  - Warm water cleaning
  - Topical steroids
    - Budésonide (Entocort®) :
      - 32 tablets = 96 mg, to be incorporated in a Carbopol 980® gel to 160 g
      - adjust to pH=5 with soude
      - apply 5 g/day during 4-6 wks, then wean progressively
  - Topical ciclosporine cream :
    - *Ciclosporine 400 mg*
    - *Liquid paraffin 30 gr*
    - *White vaseline 70 gr*
  - Topical tacrolimus application (vulva) : Protopic® bid
  - Topical estrogens
  - Dilators, surgery

GVHD

Treatment of chronic GVHD : supportive care

- **Eye**
  - **Artificial tears (eyewash, gel, ointment)**
  - **Topical steroids : Pred forte® / Maxidex ® collyre, 4 x/day**
  - **Oily ciclosporine eyewash 0.05%**
    - ***Ciclosporine 4 mg (from Neoral Sandimmun ® 100 mg/ml)***
    - ***Castor oil ad 8 ml***
  - **Pilocarpine**
  - **Occlusive eyewear**
  - **Lachrymal plug**
  - **Membranes, sclero-corneal lenses**
- **Neurologic**
  - **Treatment of polyneuropathy**
  - **Psychologist, psychiatrist**
  - **Pain management**

GVHD

Treatment of chronic GVHD : supportive care

- **Fasciitis**
  - Physical therapy
- **Muscles**
  - Exercise
  - Physical therapy
  - Cramps : diazepam (Valium®), baclofene (Lioresal®)
- **Bone : prevention of osteoporosis**
  - Ca, vit D
  - Biphosphonates, Rank-L inhibitors