# Infections tardives, déficit immunitaire et vaccination après allogreffe de moelle

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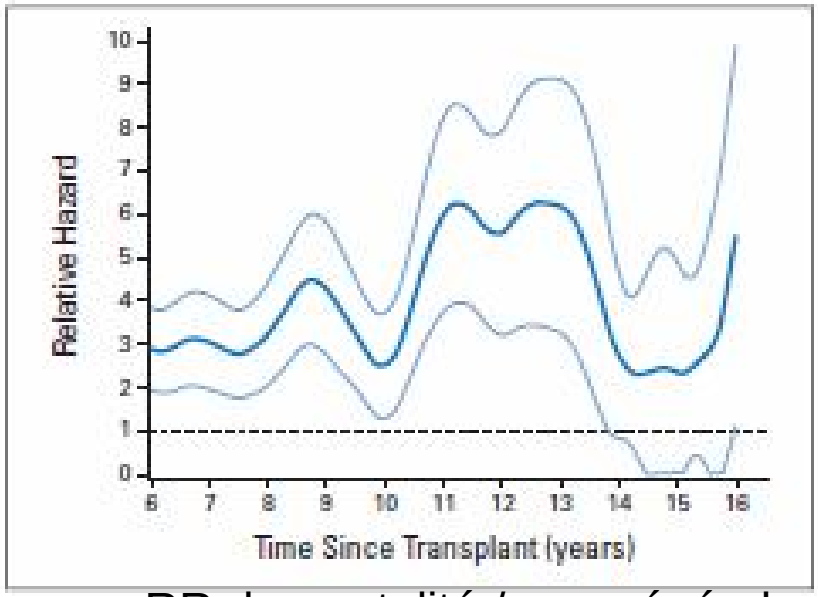
# Long terme après allogreffe de moelle

- Mortalité liée à la rechute et toxique maximale les 2 premières années puis « plateau »
- Parmi les survivants à long terme, la survie sans rechute à très long terme # 90%




RR de mortalité / pop générale

- <u>Les causes de décès:</u>
  - ✓ 40 à 50% rechute (< 10% pour la LMC)
  - ✓ 20-30% GVHD
  - ✓ **5-15% infection**
  - ✓ 2-10% second cancer
  - ✓ 5-10% défaillance d'organe

NEJM 1999. Socié. JCO 2010 Goldman. JCO 2010 Martin

# Facteurs prédictifs de mortalité tardives

- Age (moins chez l'enfant)
- cGVHD
- Statut de la maladie

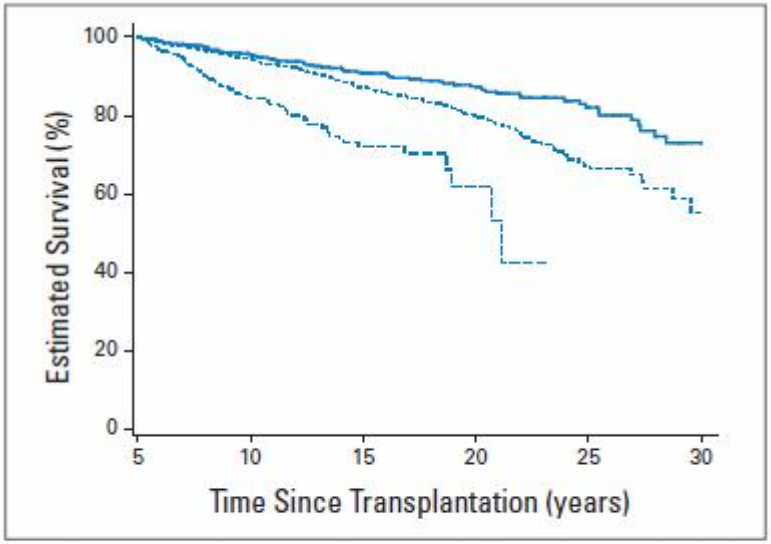
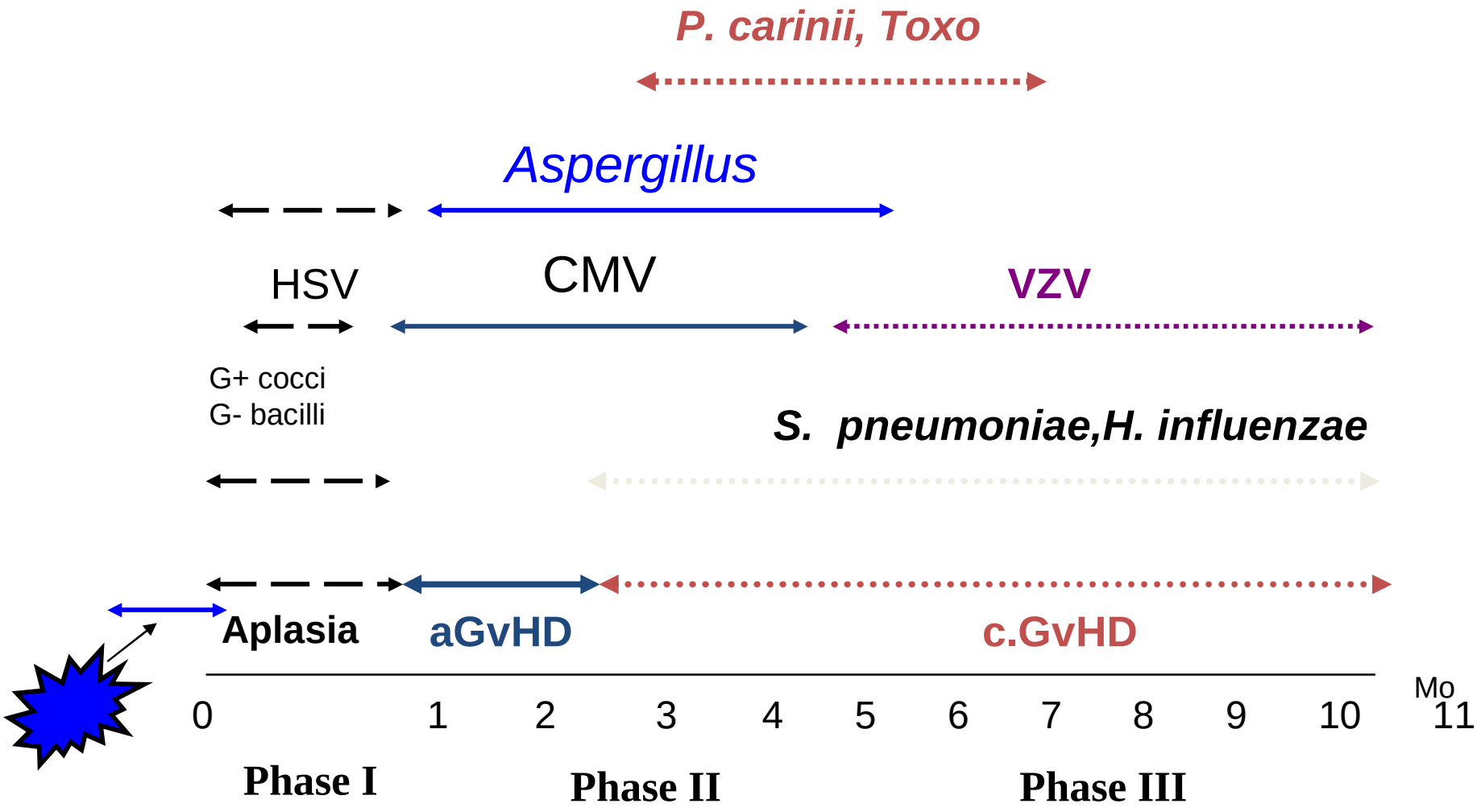



**Fig 1.** Survival and mortality rates for patients younger than age 18 years (solid line), 18 to 45 years (short-dashed line), and older than age 45 years (long-dashed line) at the time of transplantation.

JCO 2010. Martin

NEJM 1999. Socié. JCO 2010 Goldman. JCO 2010 Martin

# Infections et période postgreffe



# Bacterial infections after SCT

- Late pneumococcal infections are frequent after alloSCT: 7 to 15/1000 depending from risk factors

- Main risk factors to develop late pneumococcia are:

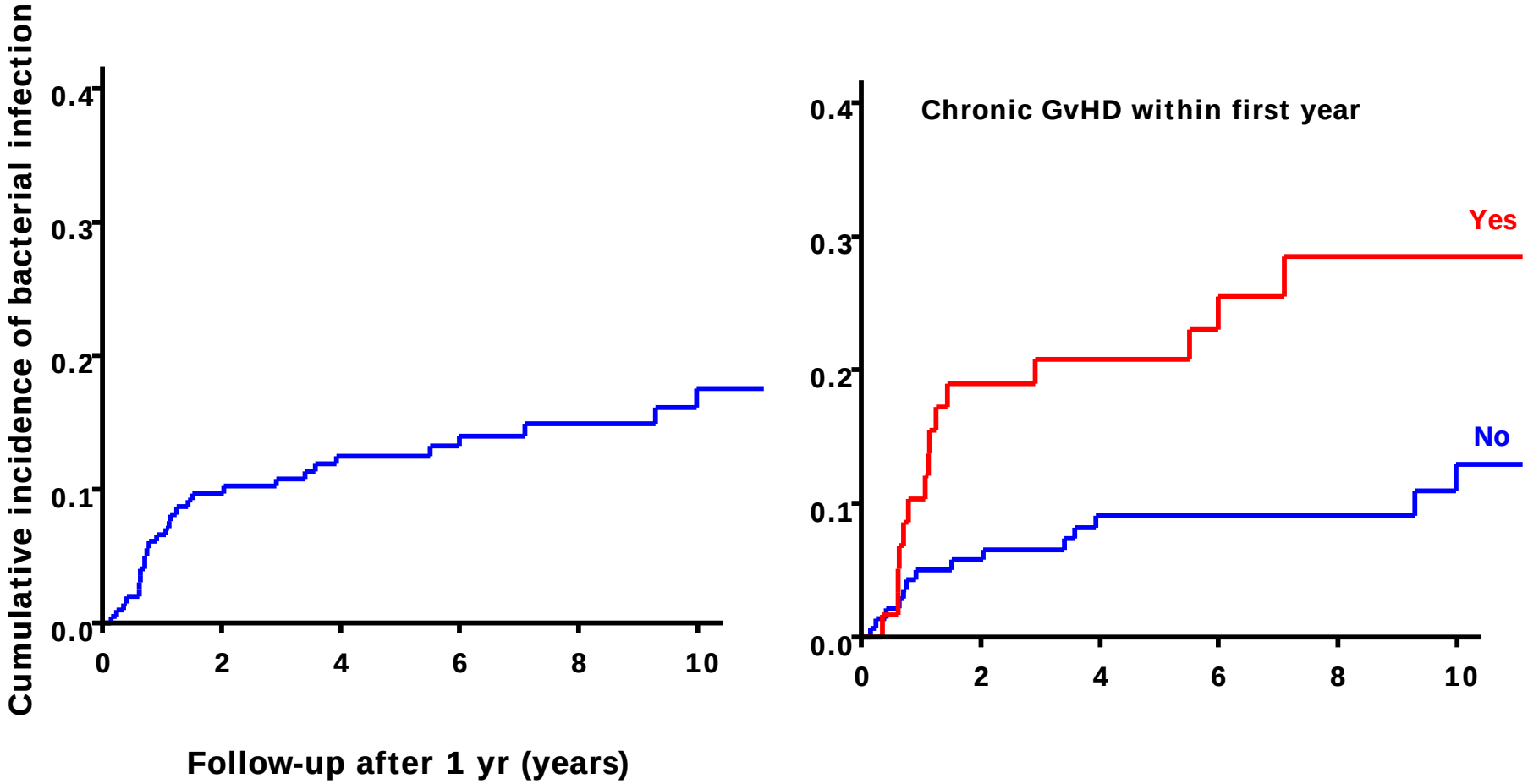
  - GVHD
  - Patients treated by corticosteroids
  - TBI

- Mortality rate for pneumococcal infection # 20%
- Penicillin and vaccin+++

BJH 2002. Engelhard. Blood 2000 Kulkarni. Medicine 2007 Youssef

# Bacterial infection and c.GvHD-associated immune deficiency

Robin et al, ***BBMT***; 2007



# Risk factors for late severe bacterial infections

| Multivariate analysis | HR (95%CI) | P |
|---|---|---|
| Irradiation in conditioning regimen | 3.11 (1.24-7.83) | 0.016 |
| Negative CMV donor to positive recipient | 2.53 (1.08-5.94) | 0.033 |
| **Extensive chronic GVHD within 1 yr** | **2.94 (1.26-6.88)** | **0.013** |

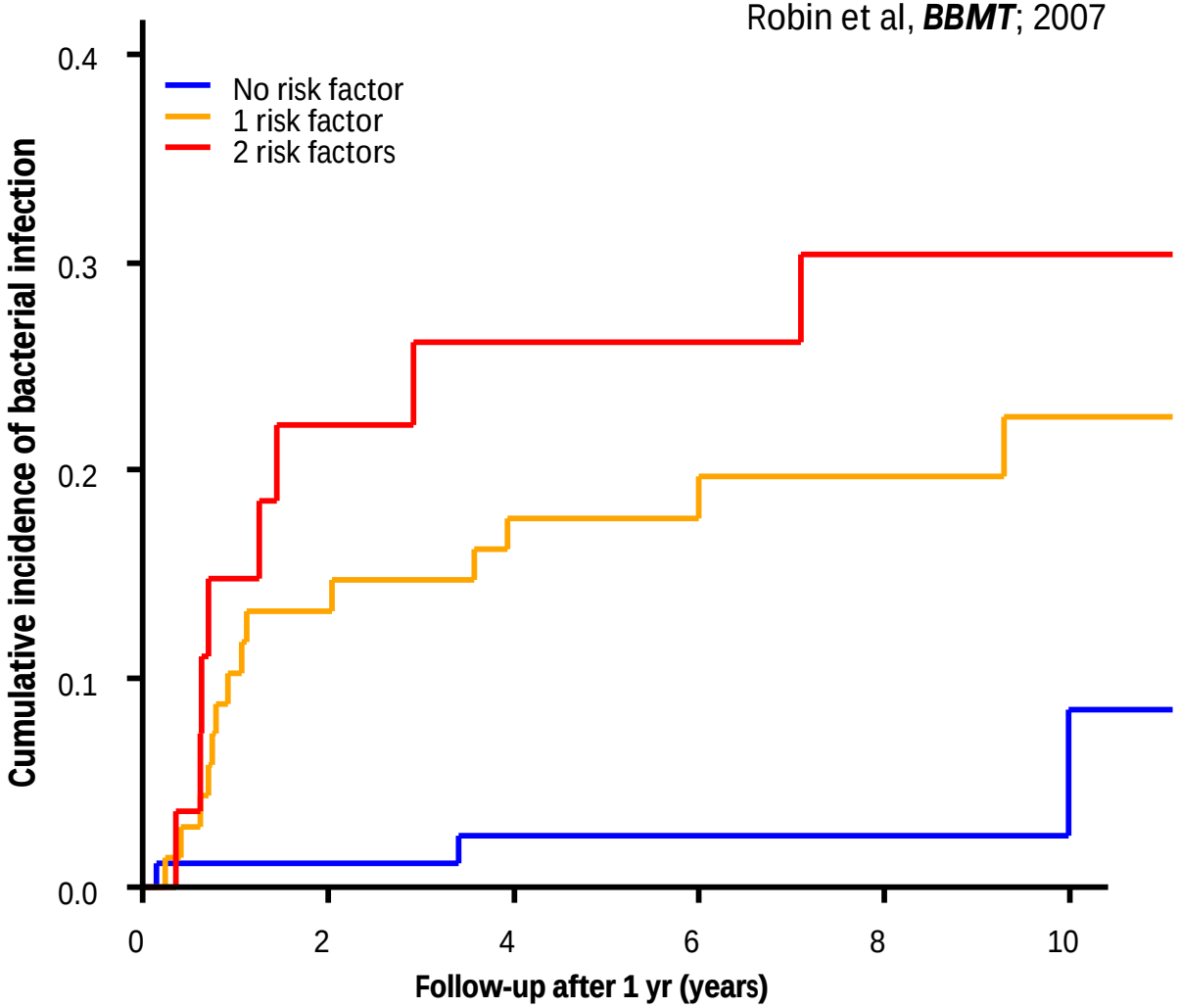
Robin et al, ***BBMT***; 2007

- ✓ Acute and/or chronic GVHD
- ✓ CMV
- ✓ Mismatched or unrelated donor
- ✓ TBI

Bjorklund et al, ***BMT***; 2007

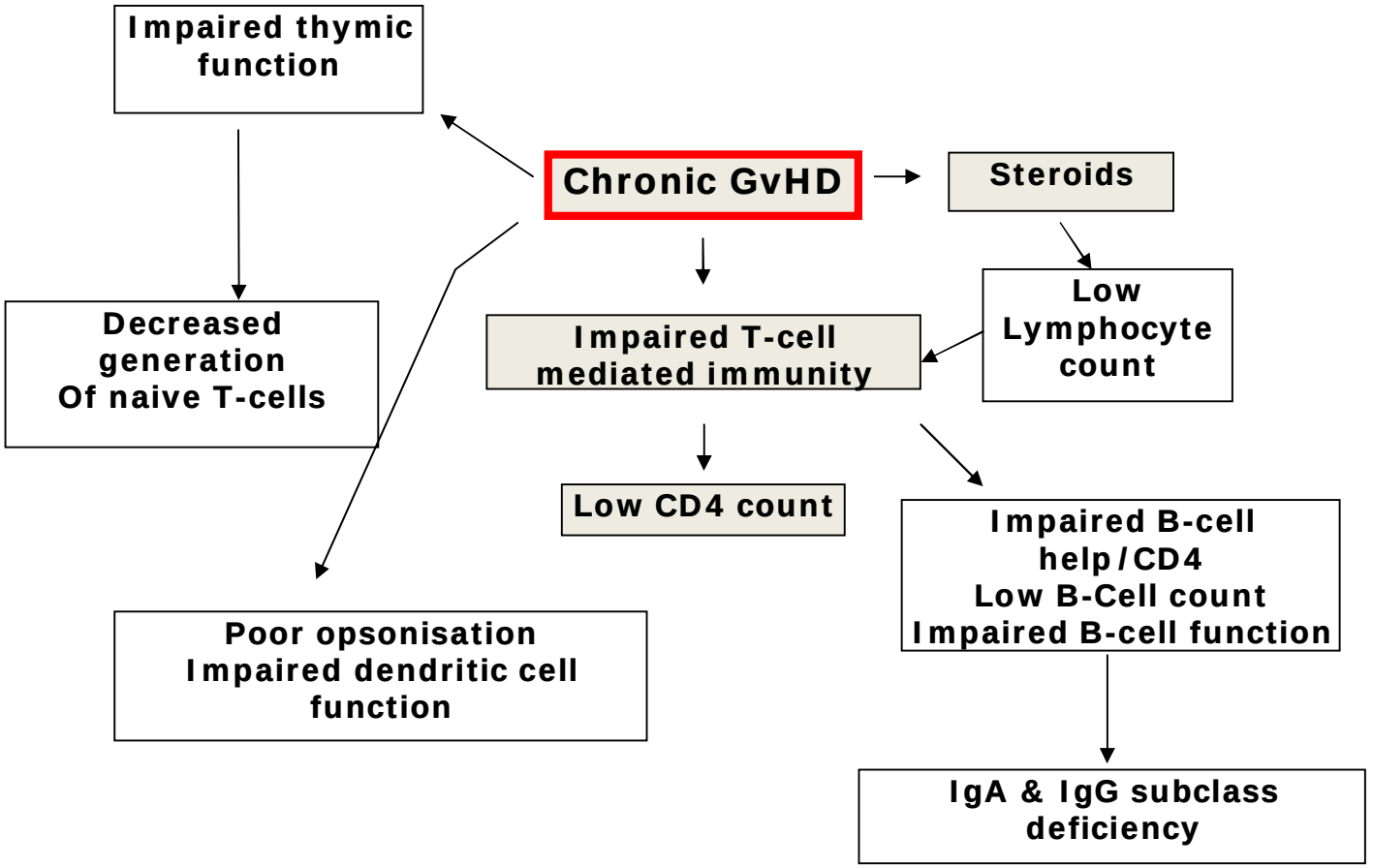
# c.GvHD-associated immune deficiency

Robin et al, ***BBMT***; 2007

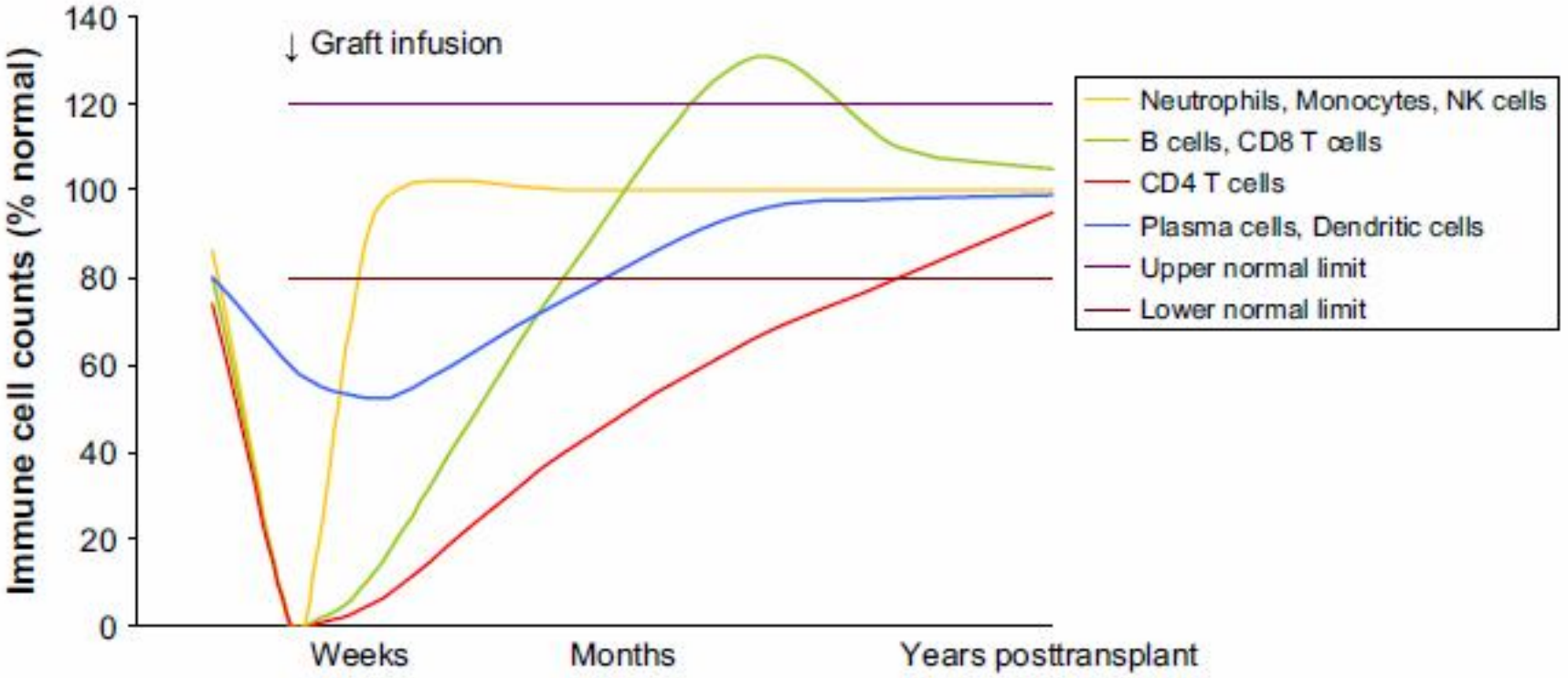


# c.GvHD-associated immune deficiency

Blood, 101, 3373-3385, 2003.



# Reconstitution hématologique



# Reconstitution immune tardive

- Etude prospective de 105 pts (MA, 84% géno-id)

| PHENOTYPE (15 mois) | % DES PATIENTS | Médiane |
|---|---|---|
| T CD4+<200µmol/L | 31% | << |
| T CD8+ < 400µmol/L | 50% | < |
| B CD19+< 200µmol/L | 39% | < |
| NK cells<100µmol/L | 38% | N |
| IgG<7gr/L | 59% | < |
| Réponse négative à toxine tétanique | 28% | nd |
| Réponse négative au CMV | 89% | nd |

BJH 2001. Maury.

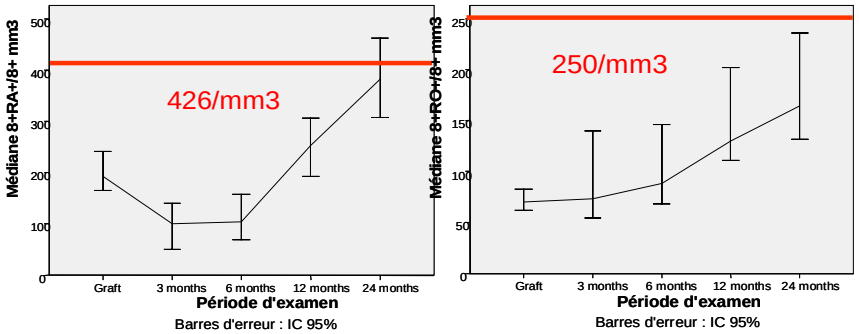
# Peripheral lymphocytes: CD4 CD8

Core. Haematologica 2010

**CD4 CD8** naive, memory and competent at 2**- year ID** are above limits value

**CD45RA** **CD45RO**

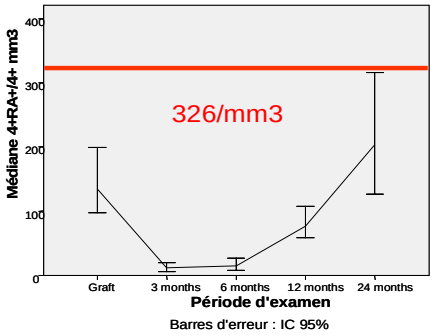
**CD8**

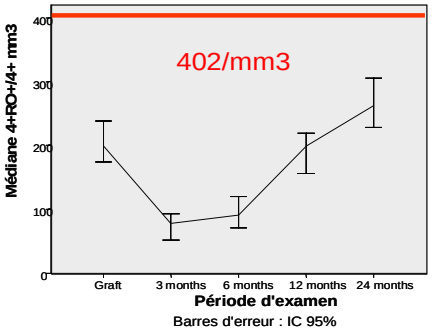


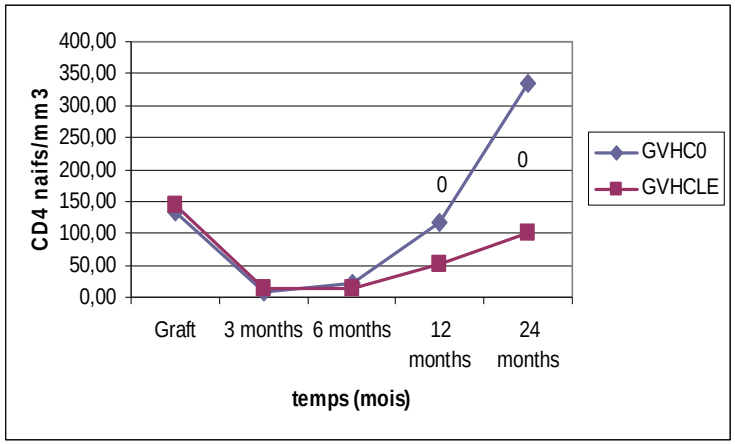




**CD4**



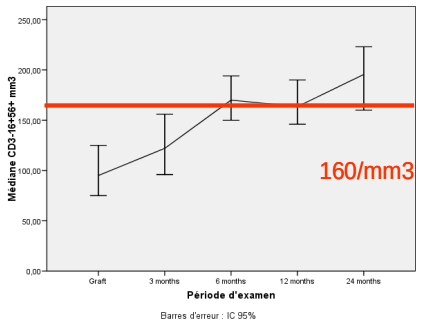




**Chronic GvHD** did not influence significantly CD8 subsets while strongly affecting the **naïve and competent CD4 subsets**

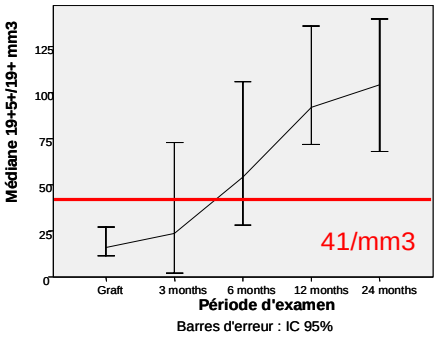
# Peripheral lymphocytes: NK. B cells

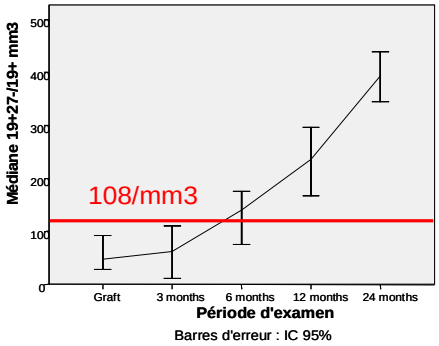
**NK** normalization at 6 months;
**B cells**: expansion of CD19+/5+ after 3 months
and persisting (till 24 mo) ID of memory B cells

**CD3-, 16+56+**

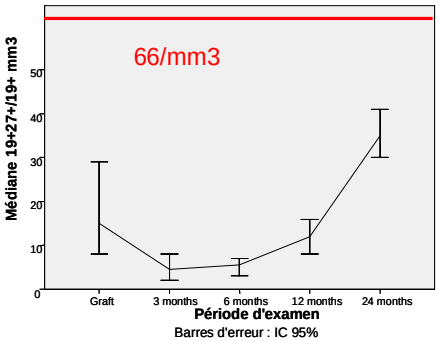



**CD19+/5+**




**CD19+/27-**




**CD19+/27+**

Core. Haematologica 2010

# Peripheral B lymphocytes & Ig

**Chronic GvHD** affects B cells reconstitution

➢Elevated numbers of immature/transitional CD21-B lymphocytes and deficiency of memory CD27+ B cells in patients with active graft-versus-host disease

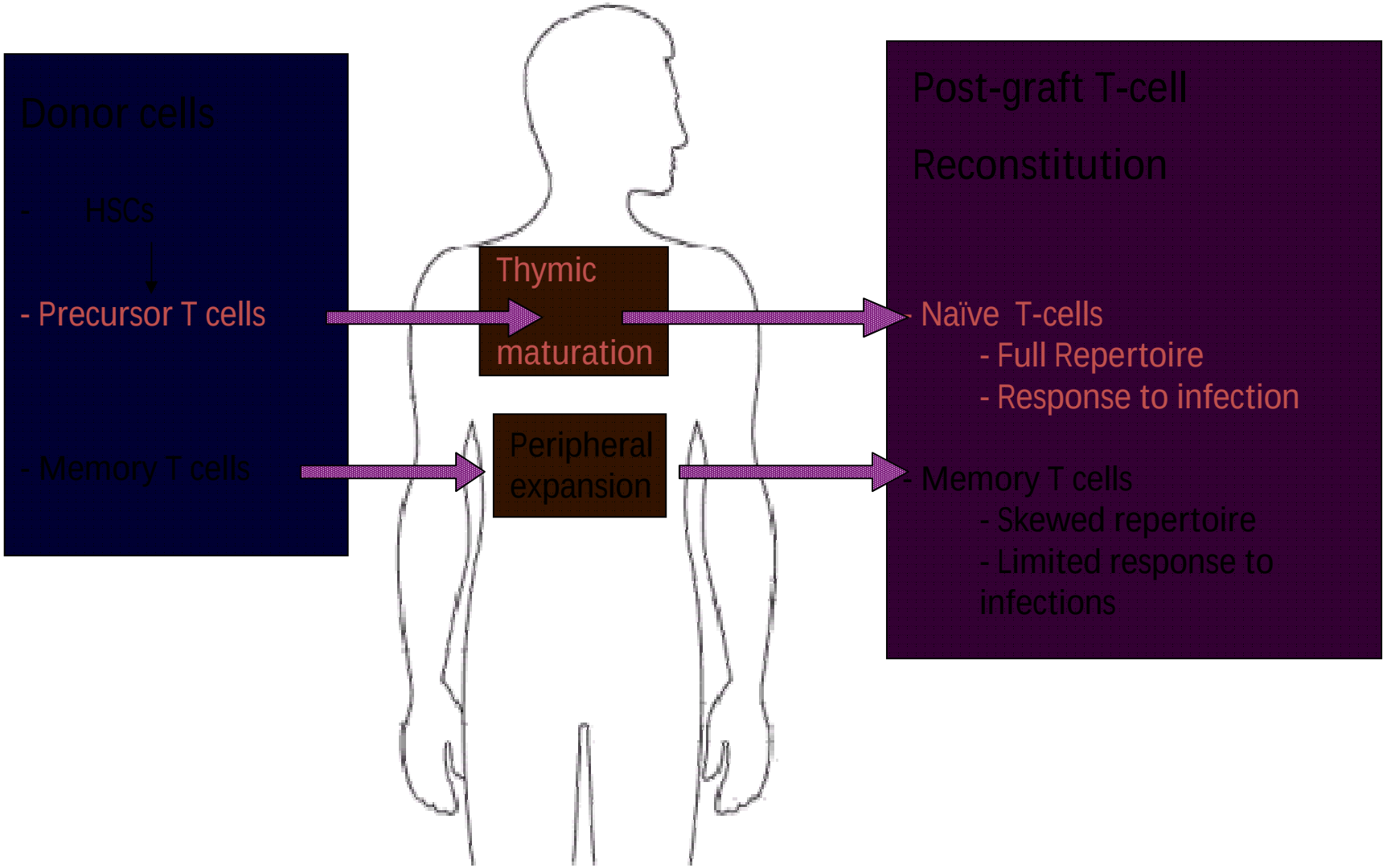
➢Number of non-class switched and class-switched memory B cells was lower in pts with GVHD

➢Lower IgG 1, IgG2, IgG4, IgA and pneumococcal antibodies in pts with GVHD

BBMT 2008. Greinix. Austria

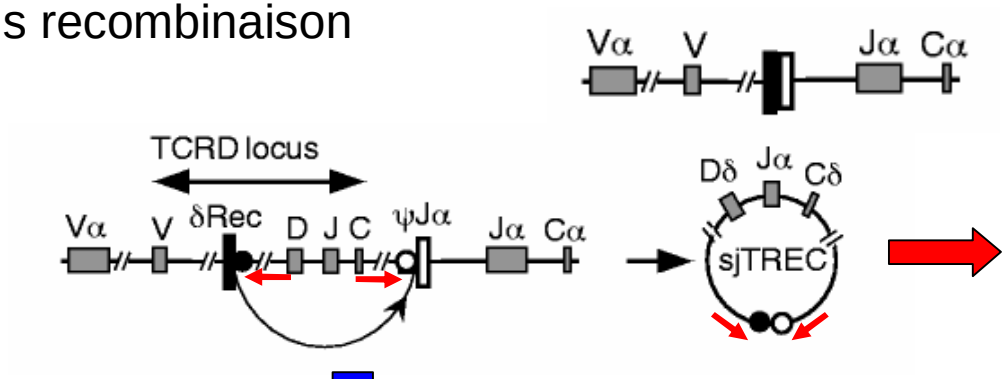
BBMT 2009. D'Orsogna

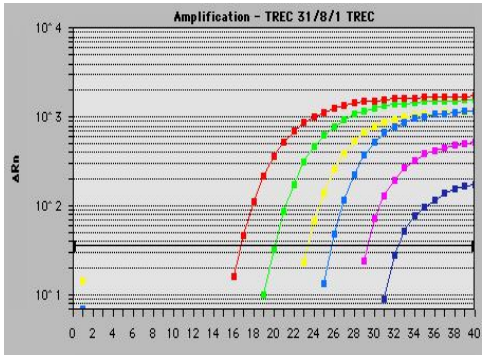
# Thymic function in HSCT



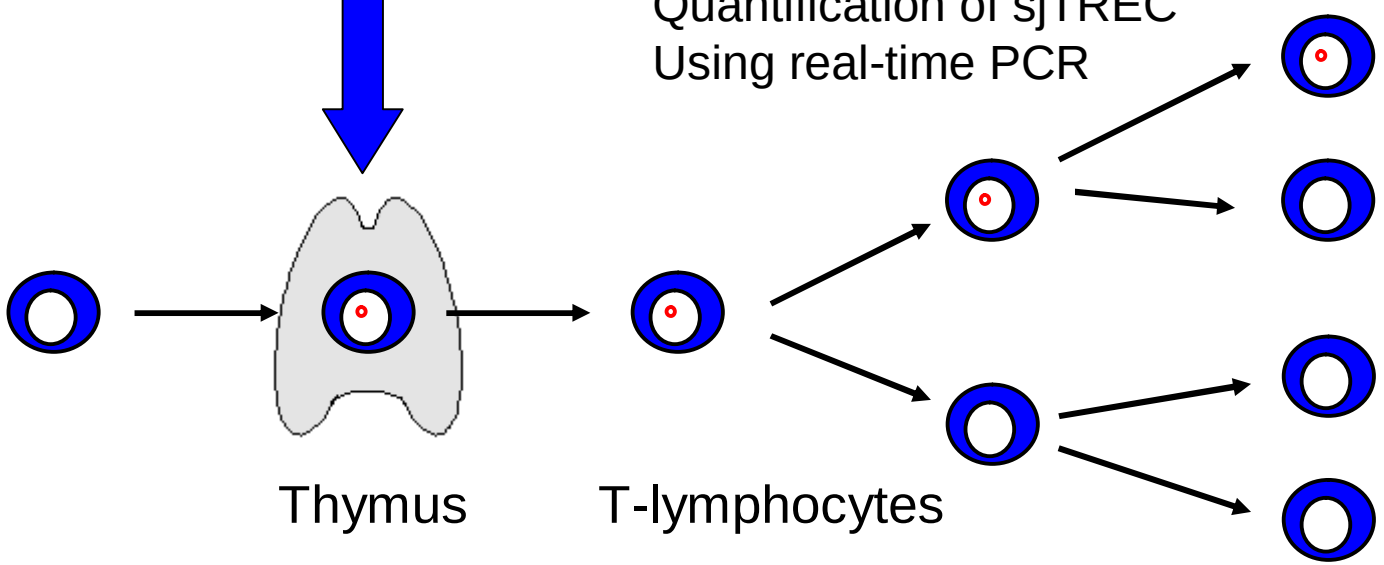
# sjTREC Assay

α locus recombinaison




Quantification of sjTREC
Using real-time PCR



Thymus

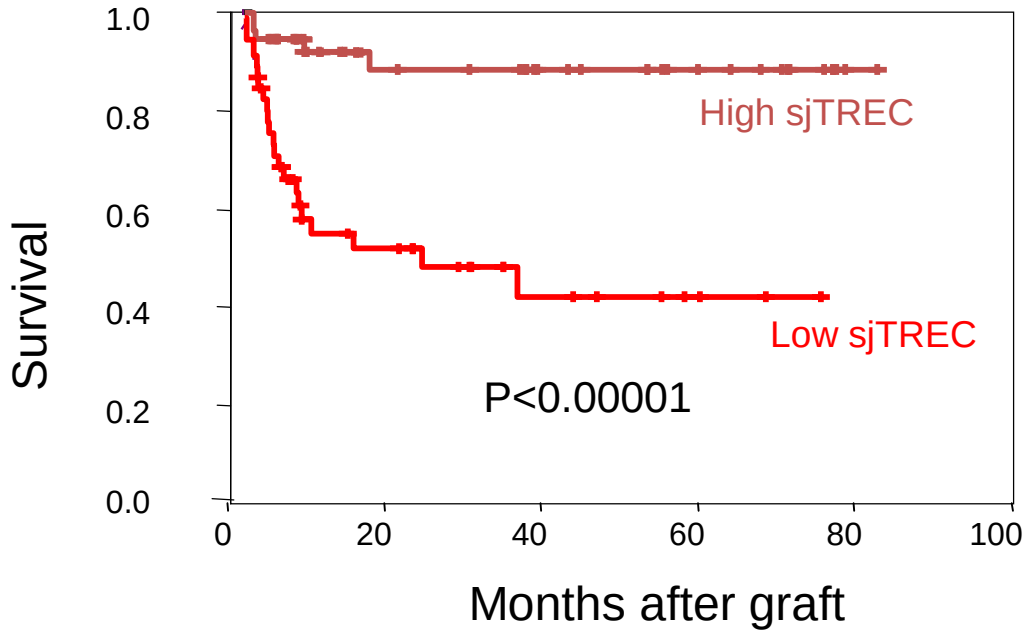
T-lymphocytes

# sjTREC before allo HSCT and survival

- 102 patients myeloablative allo-HSCT from siblings (no CB)

Threshold : 172 sjTRECs

per 150 000 CD3+




-sjTRECs in Multivariate Analysis (+ age, disease risk, CMV serology)

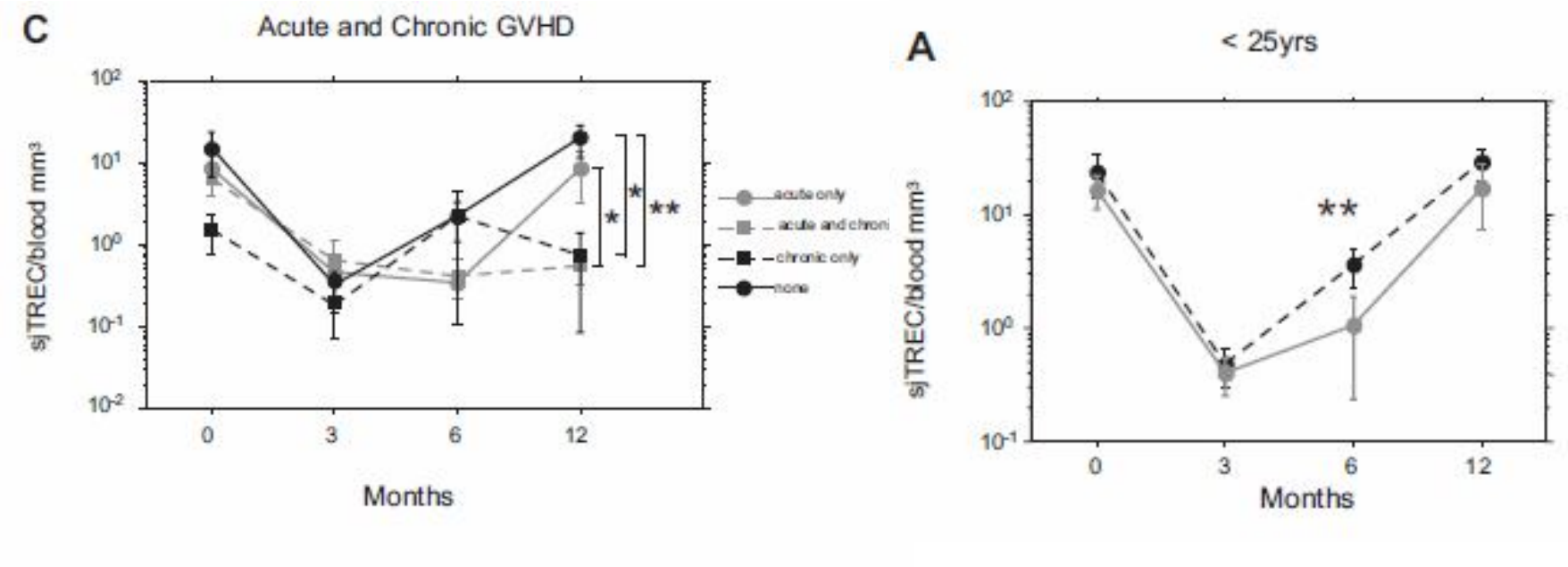
| | | |
|---|---|---|
| - on Survival | *p = 0.002* | HR = 6.6 |
| - on cGvHD | *p = 0.011* | HR = 2.2 |
| - on CMV infections | *p = 0.036* | HR = 2.8 |

*Clave et al., Blood 2005*

# Impact of GVHD on thymic function

- 93 patients myeloablative or RIC allo-HSCT from siblings (no CB)

-Age and GVHD have negative impact on recovery of thymic function




-**aGVHD delays the recovery of a fully diverse T-cell repertoire**

-the thymic impact of an episode of aGVHD could be fully reversible in younger patients

-patients developing cGVHD without a prior aGVHD episode had, at month 6, a thymic function indistinguishable from those patients without GVHD

*Clave et al., Blood 2009*

# Factors influencing immune reconstitution

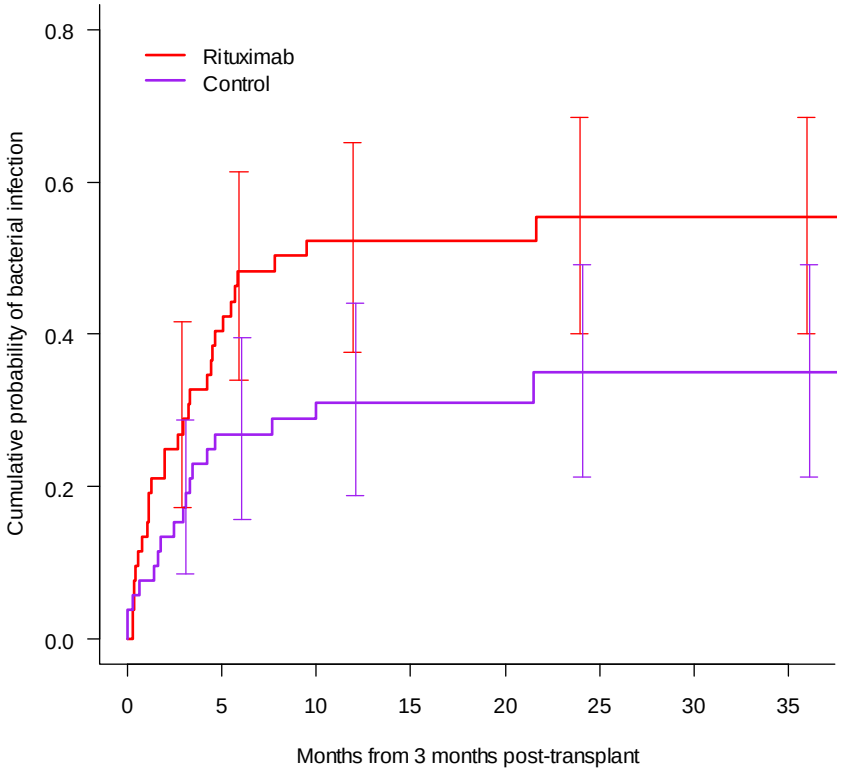
- Polymorphisme génétique ex: complement Mannose-binding lectin. Haematologica 2010. Osthoff
- Age BBMT 2006 Baron. Blood 2005 Clave
- HLA mismatch
- Type of donor (related / unrelated) BBMT 2006 Baron
- Source of stem cells
  - More infections after UCB (virus++)
  - BM vs PB: only cGVHD is important (less B cells) Haematologica 2005
  - BM vs CB: similar lymphocytes recovery Exp Hematol 2001. Moretta
- Conditioning regimen
  - Lower infections with RIC BMT 2009. Bachanova. BMT 2005. Larosa BBMT 2001
  - Similar infection and lymphocytes recovery BMT 2003. Saito

# Rituximab and bacterial infection

**Rituximab** affects B cells reconstitution

- Impaired B cells reconstitution while administered before transplantation (BMT 2008. Buser)

- Impaired B cells reconstitution, IgG secretion and risk of bacterial infection while administered after transplantation




Transplantation 2012. Petropoulou

# Corrélation « biologie & infection bactérienne»

« Unfortunately, there is currently no definitive laboratory marker of immune reconstitution that would predict infectious risk that could be used to tailor infection prophylaxis…”

Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective BBMT 2012. Tomblyn

# Corrélation « biologie & infection bactérienne»

- B cells +/- hypogamma
- Cellules B CD-21 associées à des infections sévères
- Taux de monocyte à J100
- Lymphopénie B (<200 µmol/L (37% vs 8%)
- Inversion du ratio CD4/CD8 < 1 (25% vs 0%)
- Réponse négative à toxine tétanique (33% vs 15%)

BJH 2001. Maury. Blood 2000; Storek

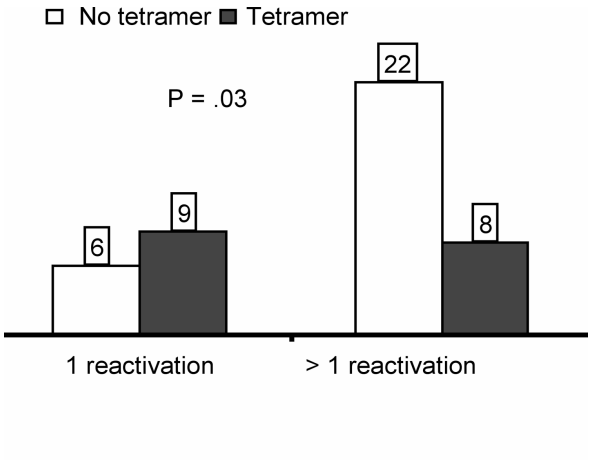
# CMV-specific immune reconstitution

*H Moins Teisserenc et al.*,
JID **2008**; 198: 818-826

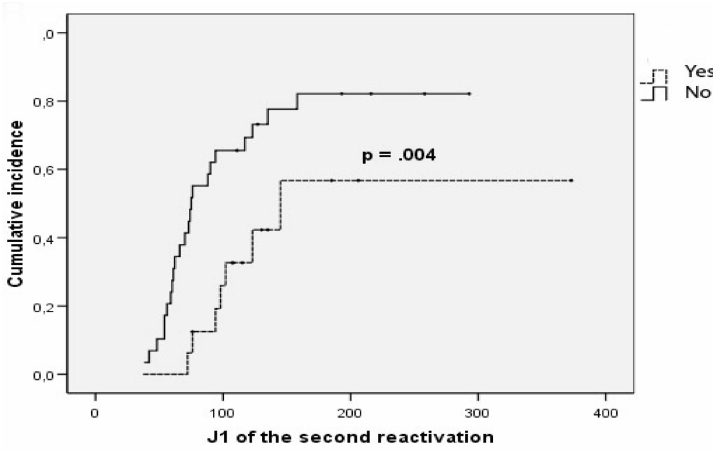
**Patterns of CMV reactivation are associated with distinct profiles of immune reconstitution after Allogeneic HSCT**

116 patients, 50% MUD → 66 seropositive patients

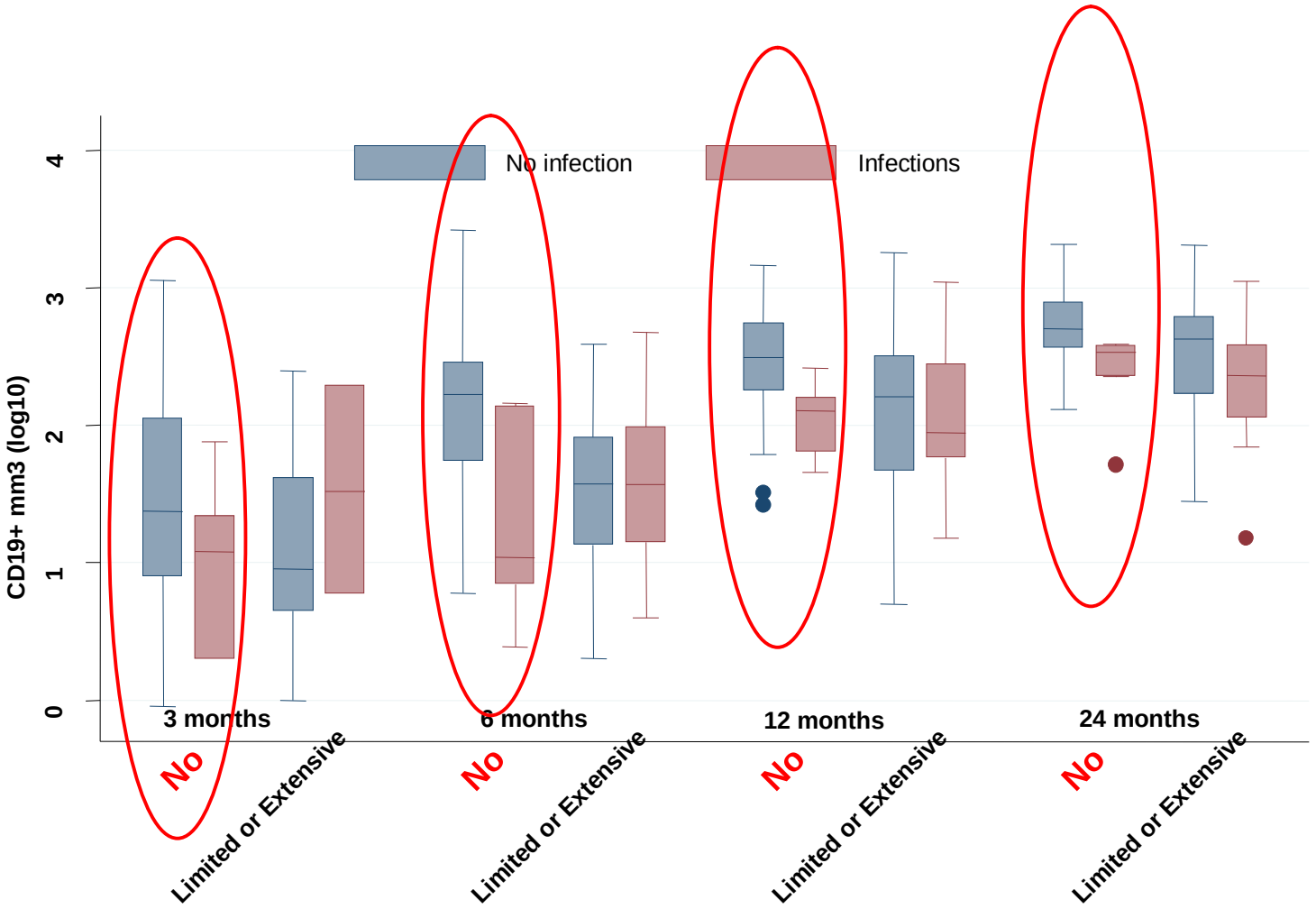
Presence of tetramer during the first reactivation




Cumulative incidence of second reactivation



**Cox models**; risk factors for the occurrence of ***late severe infections***.
Only low **B cell counts** at 6 (p=.05) & 24 mo (p=.016),
In particular if patients **did not** developed chronic GvHD




Core. Haematologica 2010

# Corrélation « biologie & infection bactérienne»

| | Survie | Mortalité non liée à la maladie | Taux d'infection |
|---|---|---|---|
| Lymphocyte < 300 (J30) | **diminuée** | **augmentée** | Non étudié |
| Lympho B 3mois | Non étudié | Non étudié | **augmenté** |
| Lympho B CD21 | Non étudié | Non étudié | **augmenté** |
| CD4+ < 200 à 3 mois | **diminuée** | **augmentée** | **augmenté** |
| CD8 à 6 mois | **diminuée** | Non étudié | |
| Ratio CD4/CD8 < 1 | Non étudié | Non étudié | **augmenté** |
| Réponse négative à la toxique tétanique | Non étudié | Non étudié | **augmenté** |
| CMV peptide spe | Non étudié | Non étudié | **CMV++** |

# Prévention des infections tardives après allogreffe de CSH

# Traitement des infections virales tardives

- Réactivation à CMV tardives possibles dépendant du terrain++, monitoring des patients à risque (ATCD+++), traitement anti-viral QS

- VZV
  - limité par prévention prolongée++ > 12 mois - Etude randomisée (Boeckh Blood 2006).
  - Prévention au moins jusqu'à l'arrêt des IS
  - La vaccination VZV ne doit pas être utilisée avant 2 ans post allogreffe (Ig et CD4+ N) et si le patient recçit encore des IS

- Vaccin hépatite B

# Prévention des infections virales tardives

- Virus respiratoires fréquents ++
- Risque d'évolution vers des Complications Pulmonaires Tardives Non Infectieuses
- Information des familles
- Vaccination des familles++ (contagion)
- D'autant plus grave que précoce postgreffe et/ou déficit immunitaire

# Traitement des infections virales tardives

- Grippe: risque vital estimé de 0 à 30% selon les séries!
- Grippe Etude EBMT (Ljungman haematologica 2011)
  - Délai médian de survenue 19 mois
  - 30% de pneumopathies
  - Facteurs de risque de dc: âge, neutropénie, infection nosocomiale

- Traitement: oseltamivir
  - Vaccination anti-grippe: 2 injections confèrent une protection équivalente aux contrôles (Haematologica 2011 Mohty), séroconversion diminuée si GVHD, proche de la greffe

# Traitement des infections virales tardives

- VRS

- Pas d'efficacité démontrée du palivuzimab en allogreffe de moelle
- Pas d'efficacité démontrée de la ribavirine en allogreffe de moelle
- Pas d'efficacité démontrée des immunoglobulines

- La seule prévention consisterait à décaller la greffe si virus respiratoire

# Prévention des infections bactériennes

- Antibioprophylaxie par pénicilline, sujet à risque++ (GVH, hypogamma, IS)
- Vaccination HIB
- Vaccination contre le pneumocoque (PCV-13) dès le 3e mois (étude rando 3e mois vs 9e mois. CID 2009. Cordonnier)
- Coqueluche
- Ne pas reporter (plus de 3 mois) les vaccinations pour les patients avec GVHD

# Prévention des infections fongiques

- Aspergillose++
- Prévention primaire pour les patients avec GVHD chronique sévère ? Une étude posa vs fluco: pas de différence d'incidence d'infection fongique mais #5% (NEJM 2007. Ullmann)
- Surveillance des pts à risque++
- Chélation en fer (Blood 2009 Pullarkat)

# Calendrier vaccinal

| Mois 3 | Mois 6 | Mois 7 | Mois 8 | Mois 18 | Mois 24 | Mois 26 |
|---|---|---|---|---|---|---|
| | DTCoq PolioHIB | DTCoq PolioHIB | DTCoq PolioHIB | DTCoq PolioHIB | | |
| Prevenar1 | Prevenar2 | | Prevenar3 | Pneumo23 | | |
| | HBV | HBV | HBV | HBV | | |
| | Grippe tous les ans | | | | | |
| | | | | | **ROR*** | **ROR*** |

*ENFANT/ADO IMMUNOCOMPETENT SEULEMENT

**Report from the International Consensus Conference on Clinical Practice in chronic GVHD** /Vaccine 2011

# Conclusions

- La reconstitution immunitaire est lente > 2 ans
- Certains patients avec GVHD chronique gardent un déficit immunitaire++
- Progrès dans la prévention anti-infectieux: anti-fongique, vaccin…
- Progrès dans l'étude des reconstitutions immunitaires (TREC, Tétramère…)
- GVHD chronique ?