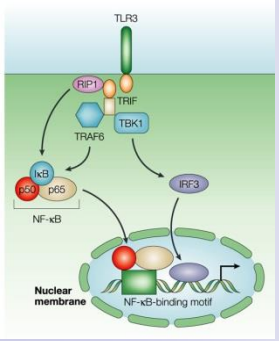
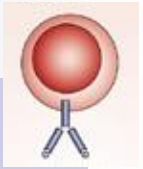
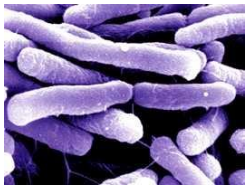
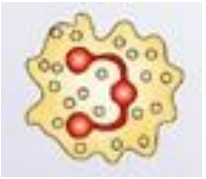








Immunodépression & infection

19è Rencontre Eveline Marckiewicz, Institut Jules Bordet

17 Novembre 2018

Dr David Grimaldi

Unité de Soins Intensifs

Hôpital Erasme ULB Bruxelles

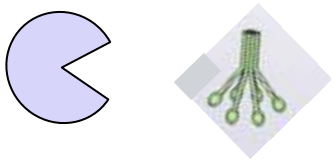
Hôpital Erasme

ULB

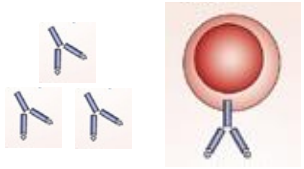
Infection susceptibility according to immunosuppression type

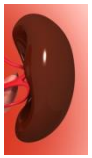
Humoral deficiency

Complement system



Antibodies B-cells

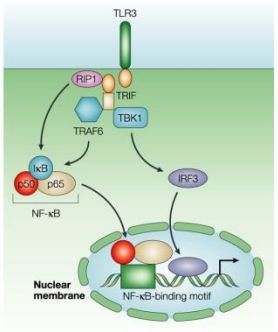




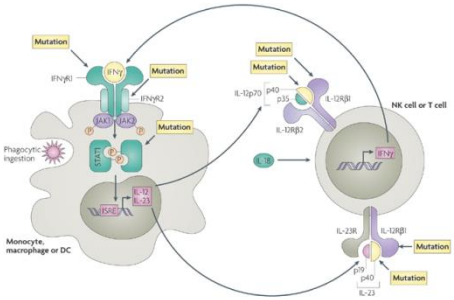
Splenectomy

Signaling impairment

TLR 3



IFN-γ
IL-12



C3 : pneumococcus

C5- C9 : meningococcus

Enterovirus

Encapsulated bacteria (pneumococcus, H. influenzae b, Salmonella sp.)

URTI (IgA deficiency)

HSV encephalitis

Mycobacteria

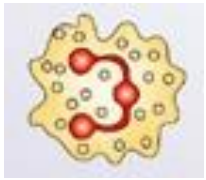
Salmonella sp.

Infection susceptibility according to immunosuppression type

Innate immune cells

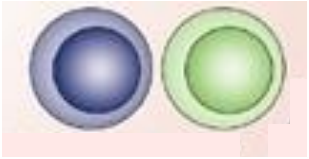
Monocytes
Macrophages

Polymorphonuclears

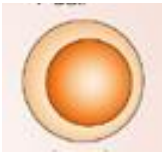


Adaptive cells

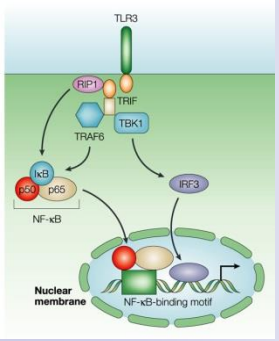
$CD4^+$ T-cells

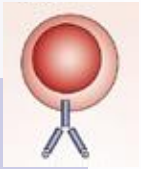


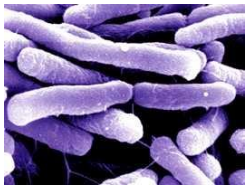
$CD8^+$ T-cells
(cytotoxicity)

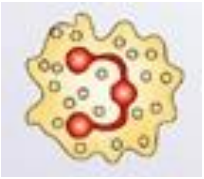


Legionnella Mycobacteria Pseudomonas	Pyogenic bacteria: - S. aureus - P. aeruginosa - … Invasive Aspergillosis Candidemia	Herpes virus (HSV, CMV, HHV6) Candidosis Pneumocystis Toxoplasmosis Mycobacteria	Viral infection EBV CMV (HSV, HHV6) Intracellular bacteria Mycobacteria





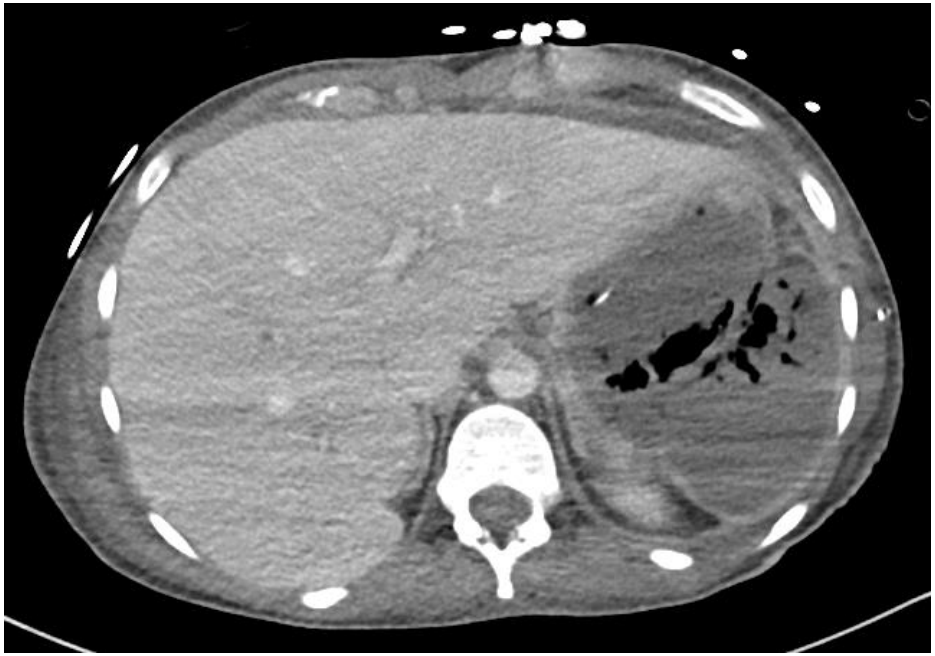




Sepsis & Immunodépression

Clinical vignette

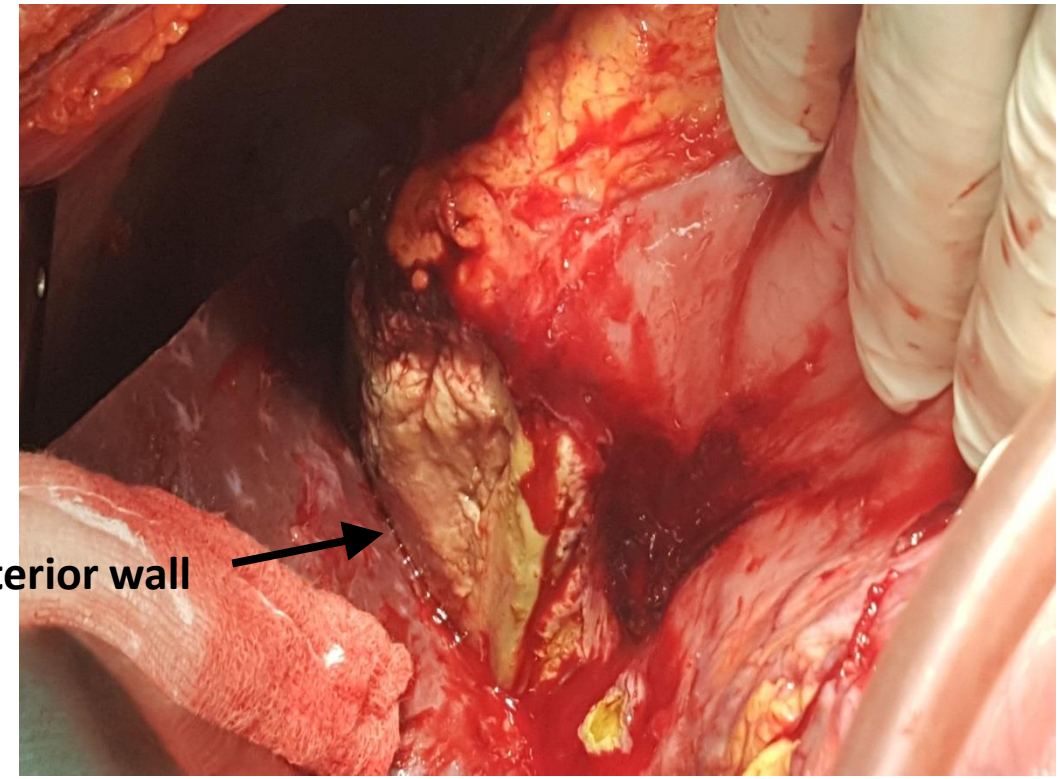
- 30 y.o. women - severe blunt pelvic trauma- haemorrhagic shock
- Day 5: septick shock related to Gram negative cellulitis
- Day 8: VAP
- Day 15-20: vomiting – Gastroscopy: localized gastric necrosis
- Day 22: CT scan



Grimaldi et al. Lancet Infectious Dis 2017

Clinical vignette

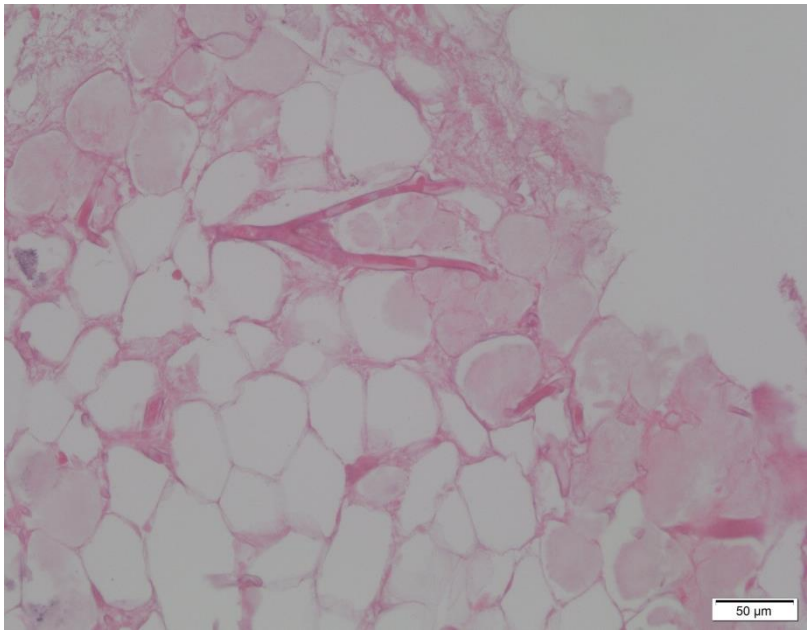
- Gastric mucosal biopsy (day 18): invasive non septate hyphae
- Liposomal amphotericin & posaconazole started
- Progressive degradation, fever, mechanical ventilation
- Surgical exploration day 22: gastric perforation
- Total gastrectomy and splenectomy

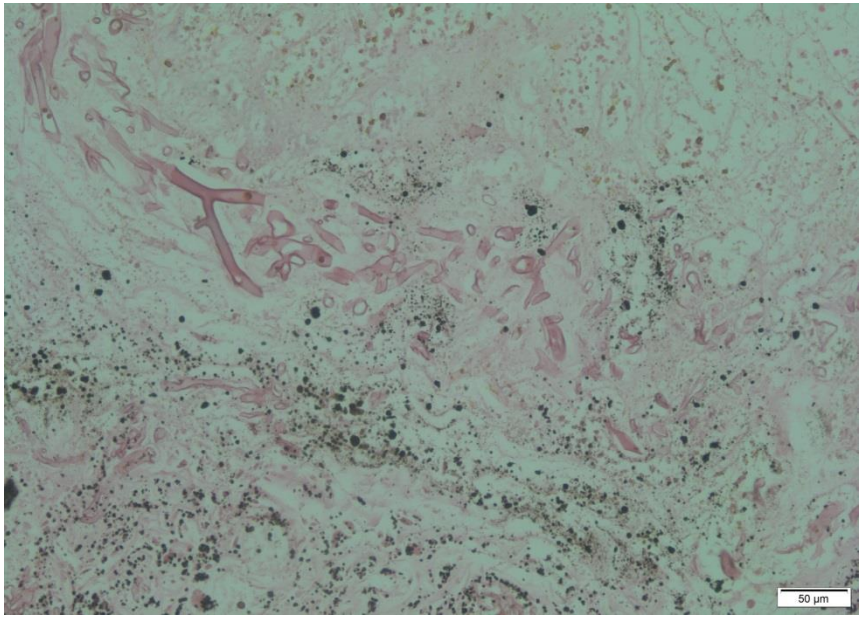


Provided by Dr Katzanos

Clinical vignette

- **Histopathological exam:**
  - **confirmed invasive mucormycosis**
  - **positive vascular margin**
  - **positive peritoneal margin**





Provided by Pr Demetter

Immune function workshop

- No previous infection
- No familial history
- Normal leukocyte count, no neutropenia
- Moderate lymphopenia 0.66 G/L
  - 0.43 CD4+
  - 0.07 CD8+ cells

Le patient septique est-il immunodéprimé ?

Risque infectieux accru

&

altérations Immunitaires

Le patient post-septique est-il immunodéprimé ?

- **Infections bactériennes nosocomiales (PAVM)**

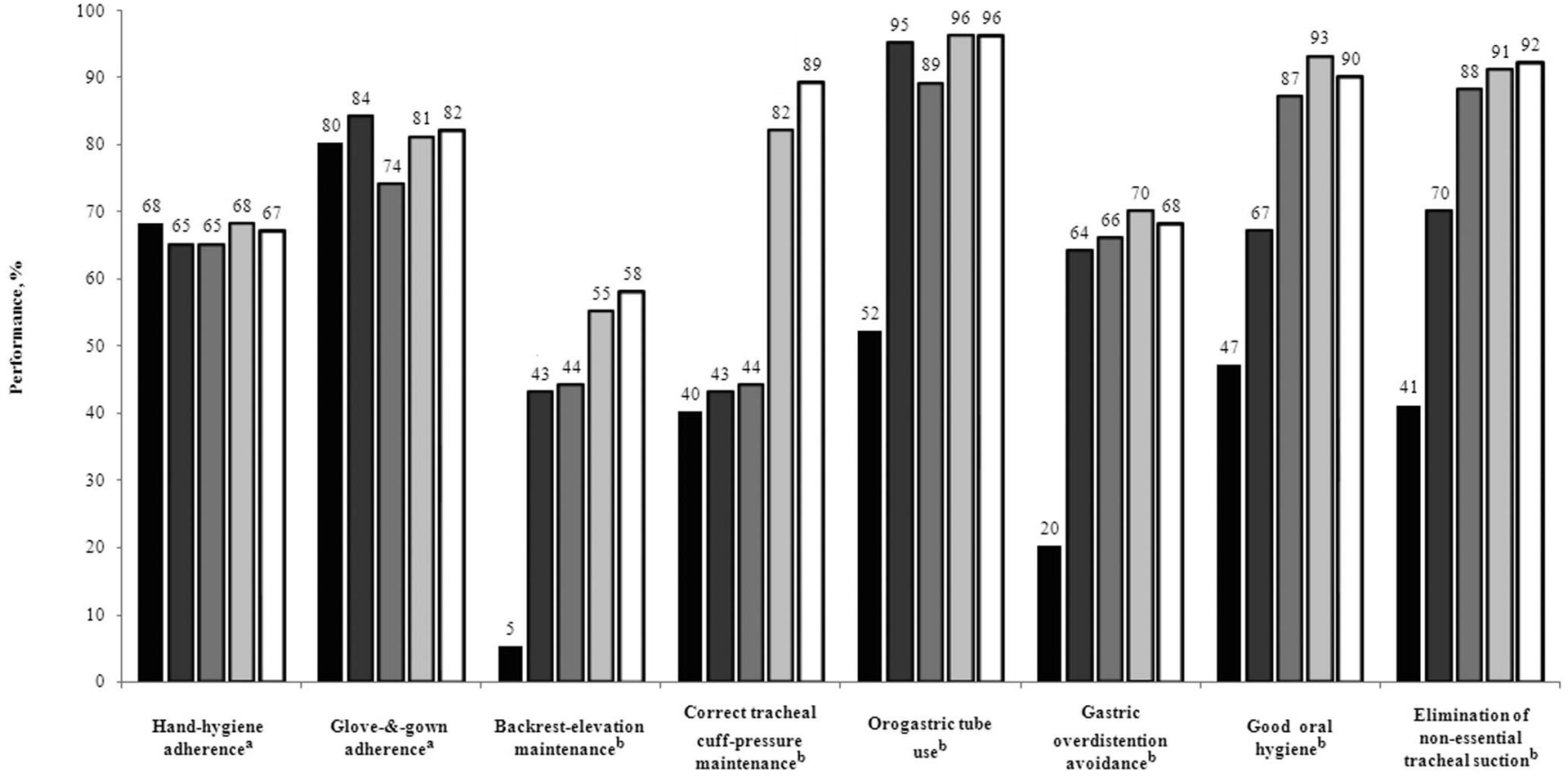
  Pseudomonas, Acinetobacter, Stenotrophomonas, Enterococcus

CID 2010:51 (15 November)

MAJOR ARTICLE

Long-Term Impact of a Multifaceted Prevention Program on Ventilator-Associated Pneumonia in a Medical Intensive Care Unit

Lila Bouadma,[1] Emmanuelle Deslandes,[2] Isabelle Lolom,[3] Bertrand Le Corre,[1] Bruno Mourvillier,[1] Bernard Regnier,[1] Raphael Porcher,[2] Michel Wolff,[1,4] and Jean-Christophe Lucet[3]



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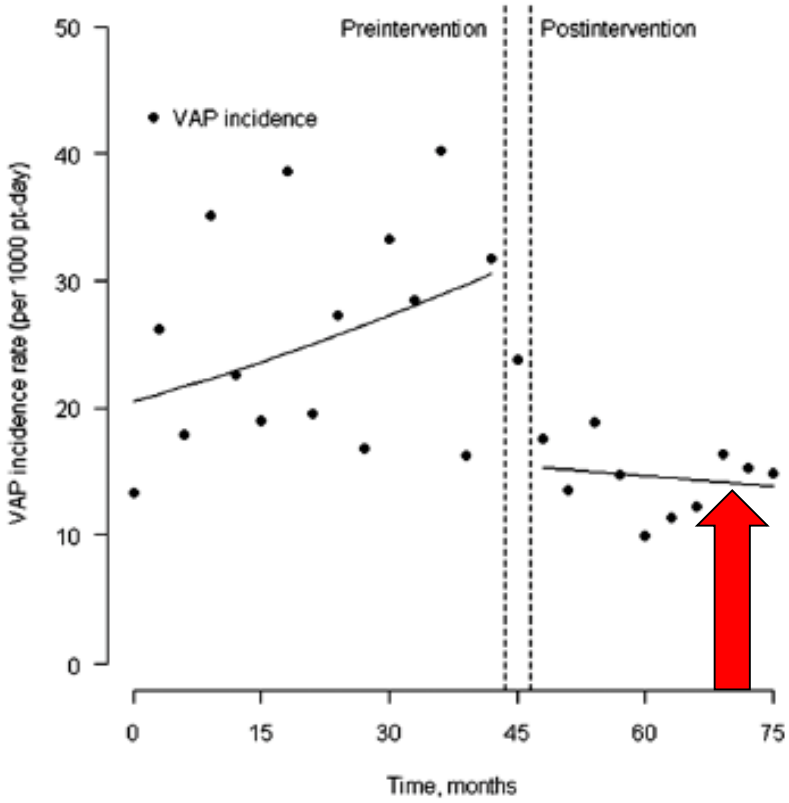
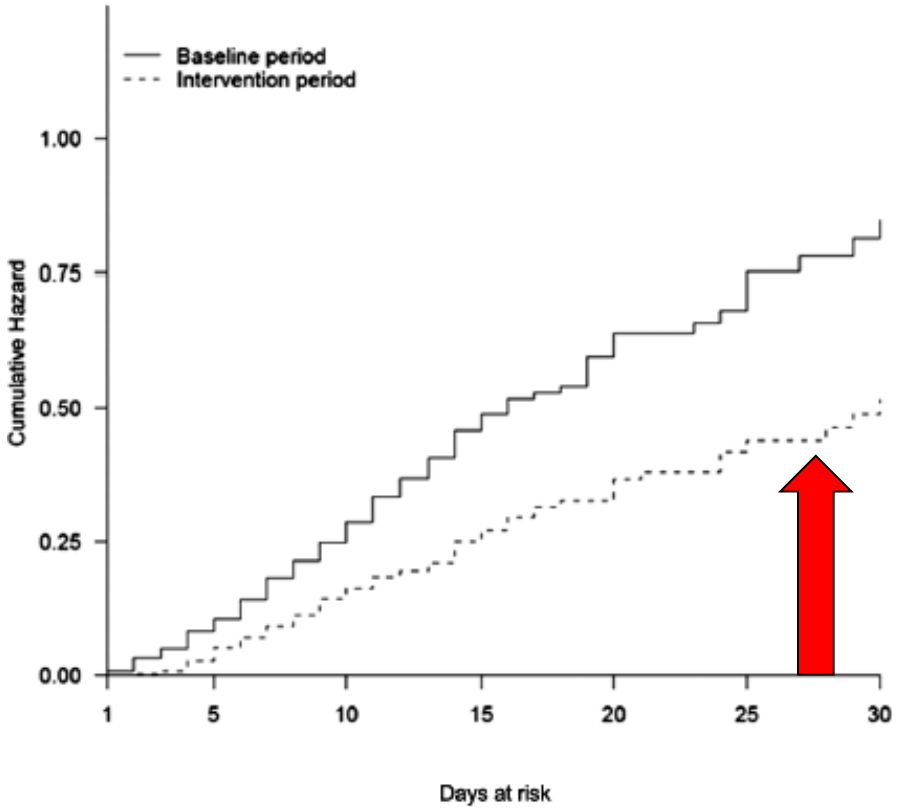




Le patient post-septique est-il immunodéprimé ?

- **Infections bactériennes nosocomiales**

  Pseudomonas, Acinetobacter, Stenotrophomonas, Enterococcus

- **Susceptibilité aux infections fongiques invasives**
  - **Candidoses** ***(Leroy et al. CCM 2009)***
  - **Aspergilloses** ***(Hartemink et al. ICM 2003)***

Intensive Care Med (2003) 29:2068–2071
DOI 10.1007/s00134-003-1778-z

BRIEF REPORT

Koen J. Hartemink
Marinus A. Paul
Jan Jaap Spijkstra
Armand R. J. Girbes
Kees H. Polderman

Immunoparalysis as a cause for invasive aspergillosis?

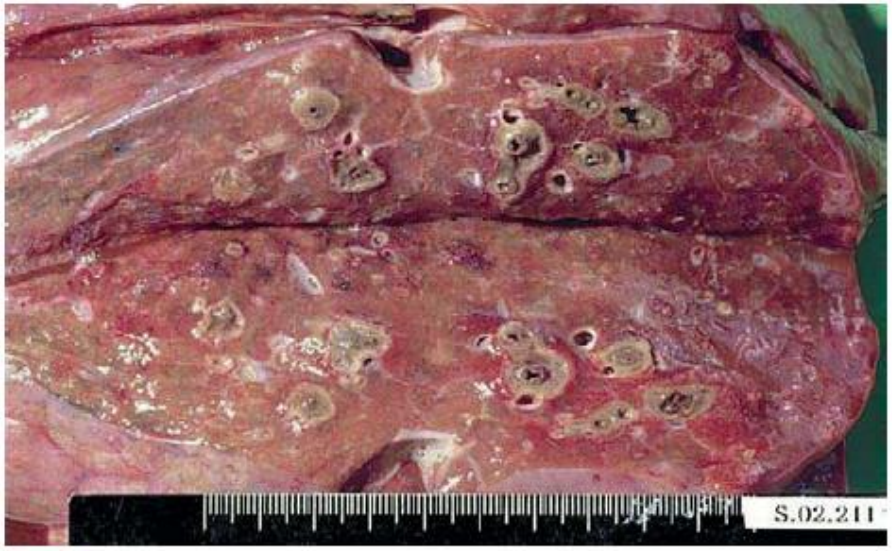


Fig. 1 Cross-section of the lung of patient A. Macroscopic view of extensive mycotic ulcerative lesions and cavities in the lung

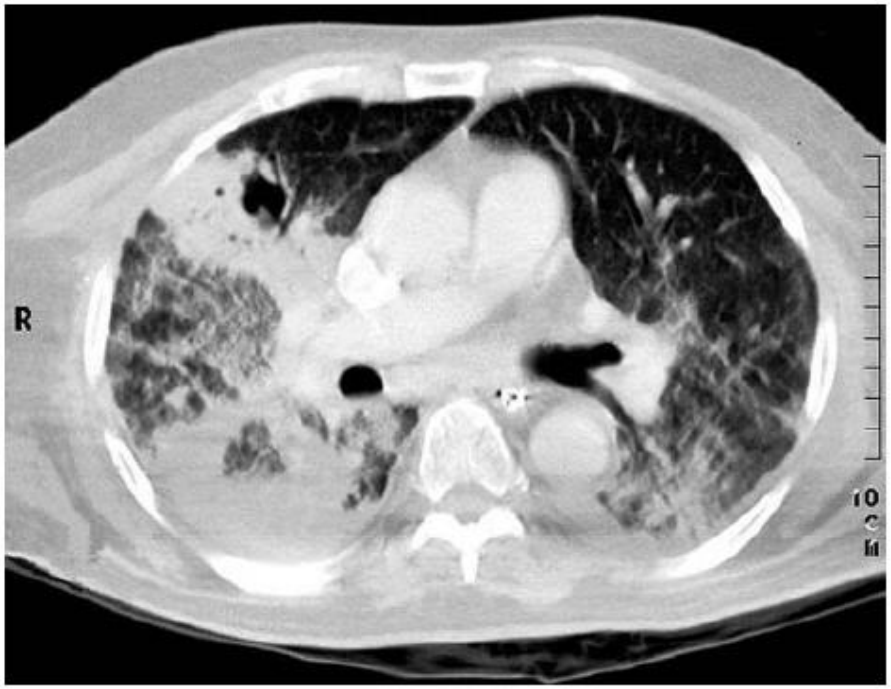


Fig. 2 CT scan of the thorax of patient D. A cavity within a consolidation, highly suspect for aspergilloma, is visible in the pectoral segment of the right upper lobe

RESEARCH Open Access

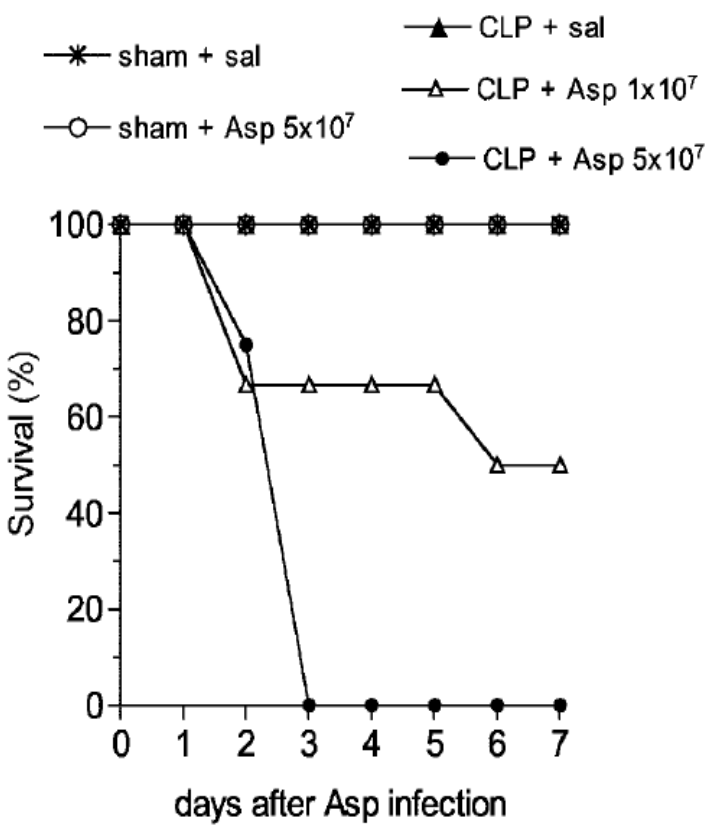
CRITICAL CARE

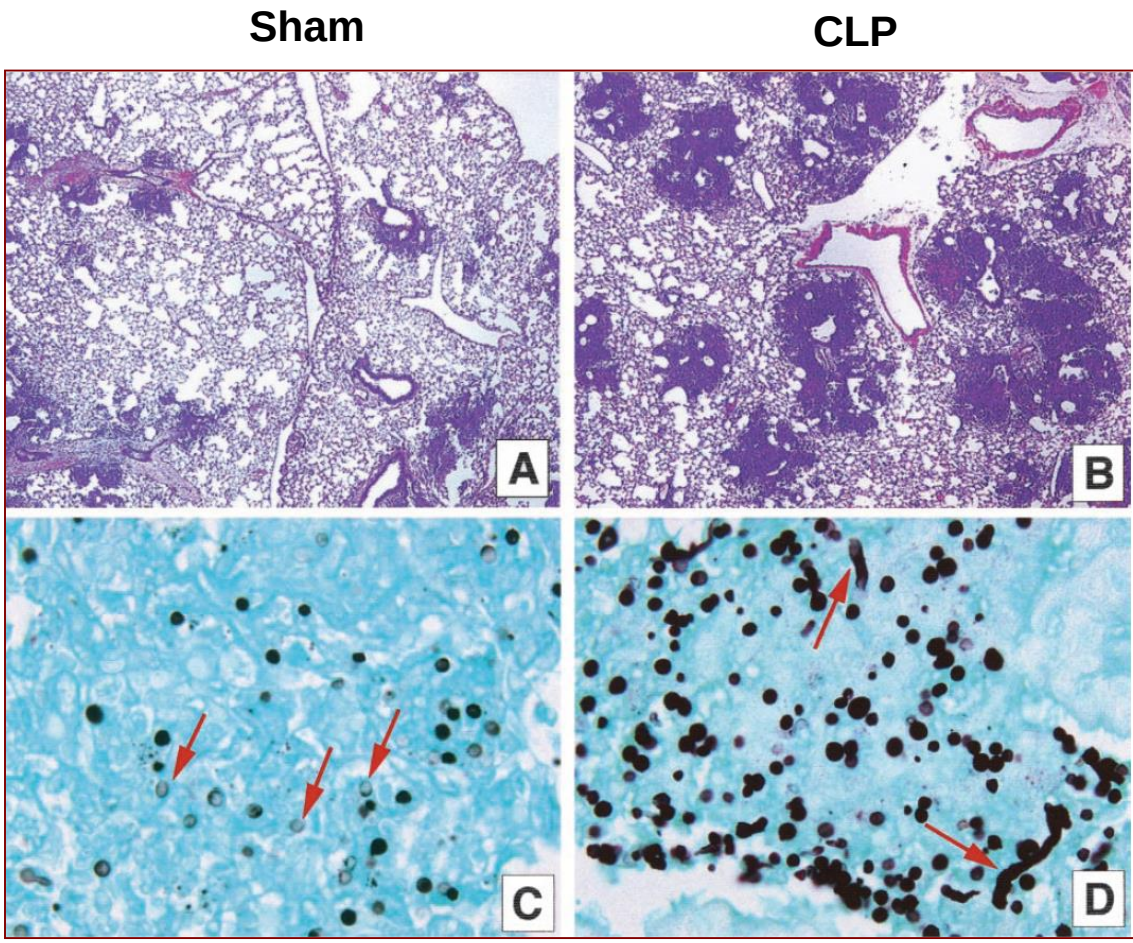
Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes

	All patients ($N = 563$)	Proven IA ($n = 94$)	Putative IA ($n = 203$)	Colonization ($n = 266$)
Age, yr	61 ± 17	60 ± 13	62 ± 16	61 ± 18
Male, *n* (%)	341 (61)	54 (57)	127 (63)	160 (60)
BMI, kg/m^2	24 (21 to 27)	24 (21 to 26)	23 (20 to 27)	25 (22 to 28)
Underlying conditions, *n* (%)				
No underlying disease	76 (14)	4 (4)[b]	11 (5)[b]	61 (23)
COPD	174 (31)	22 (23)[#]	80 (39)[b]	72 (27)
Chronic heart failure	55 (10)	8 (9)	19 (9)	28 (11)
Diabetes	92 (16)	19 (19)	33 (16)	40 (15)
Solid tumor	58 (10)	13 (14)	21 (9)	24 (9)
Hematologic cancer/BMT	48 (8)	15 (16)[b]	31 (15)[b]	6 (2)
Neutropenia	40 (7)	5 (5)[b]	18 (9)[b]	3 (1)
Radiotherapy/chemotherapy	53 (9)	12 (13)[b]	33 (16)[b]	8 (3)
Solid organ transplant	56 (10)	19 (20)[b]	28 (14)[b]	9 (4)
Immunosuppressive drugs	59 (11)	27 (29)[b#]	25 (12)[b]	7 (3)
HIV	5 (1)	1 (1)	1 (1)	3 (1)
Liver disease	40 (7)	13 (14)[b]	14 (7)	13 (5)
Chronic hemodialysis	22 (4)	3 (3)	8 (4)	11 (4)
Smoking	88 (16)	15 (16)	28 (14)	45 (17)
Alcohol abuse	54 (10)	9 (10)	16 (8)	29 (11)

Taccone et al. Crit Care 2015

Post septic mice are highly susceptible to aspergillosis





Benjamim, *Am J Pathol 2003*

Le patient post-septique est-il immunodéprimé ?

- **Infections bactériennes nosocomiales**

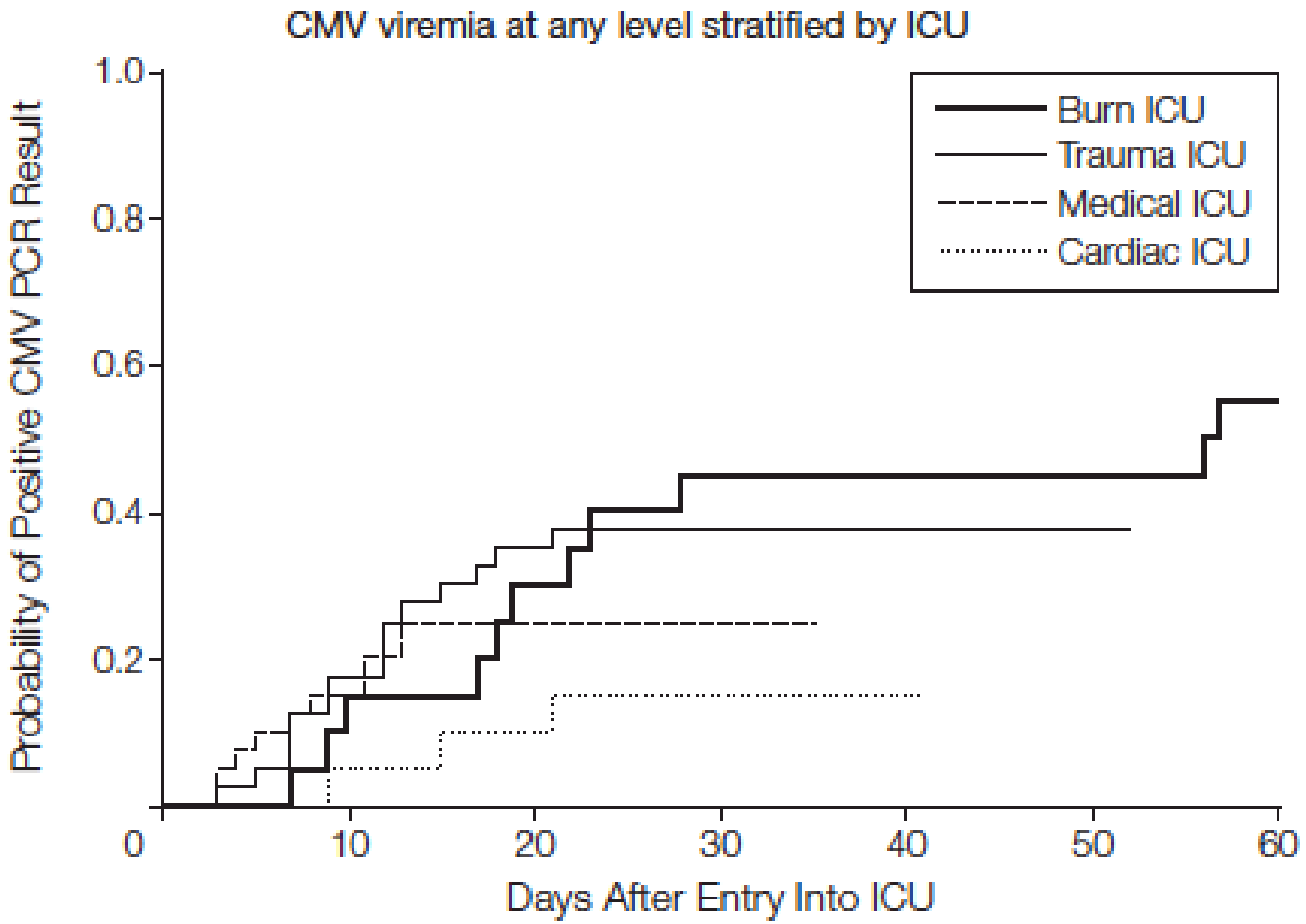
  Pseudomonas, Acinetobacter, Stenotrophomonas, Enterococcus

- **Susceptibilité aux infections fongiques invasives**
  - **Candidoses** ***(Leroy et al. CCM 2009)***
  - **Aspergilloses** ***(Hartemink et al. ICM 2003)***

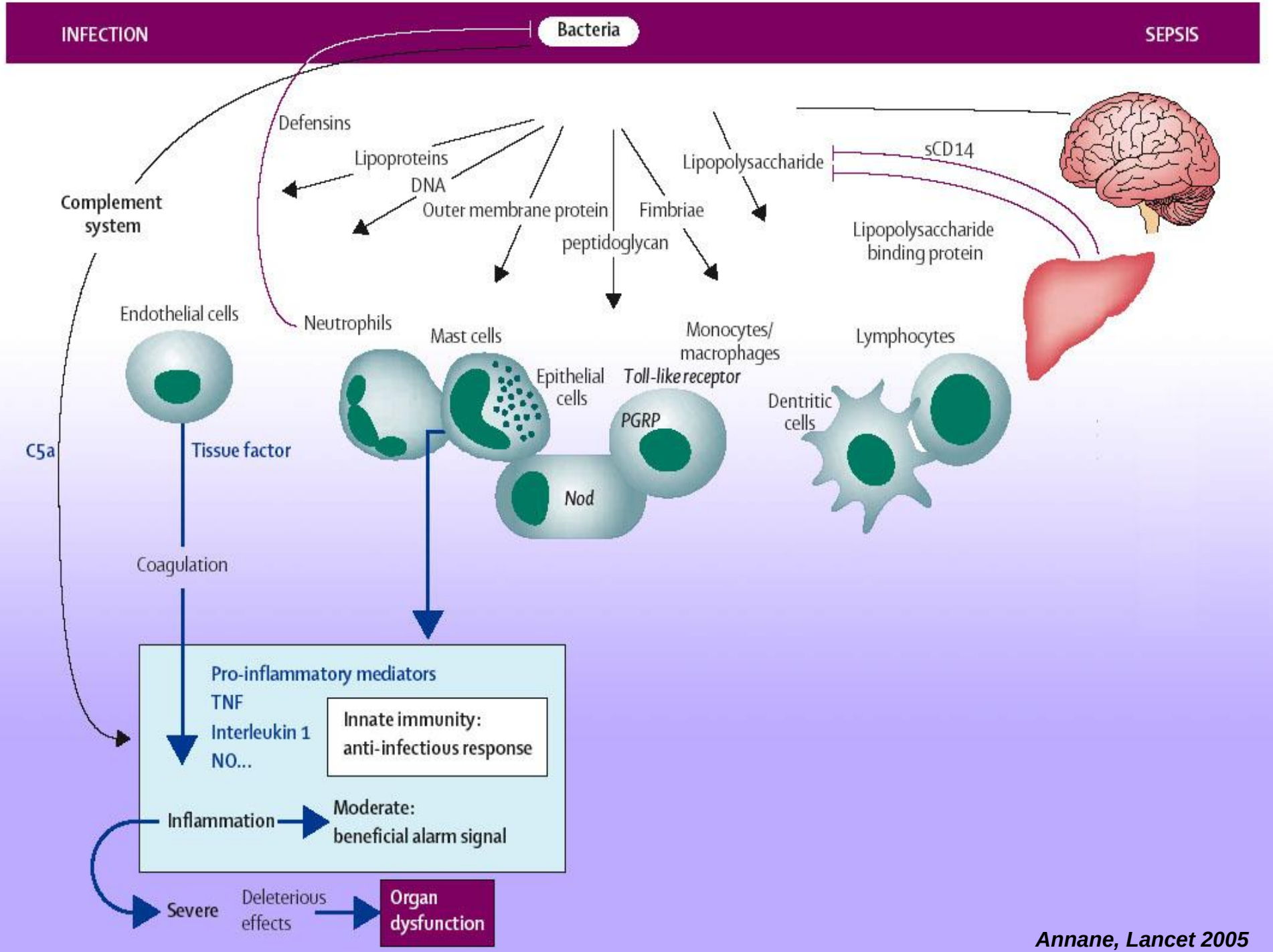
- **Réactivations de virus du groupe herpes**
  - **HSV** ***(Luyt et al. AJRCCM 2007)***
  - **CMV** ***(Papazian et al. CCM 2007, Limaye et al. JAMA 2008)***

Cytomegalovirus Reactivation in Critically Ill Immunocompetent Patients

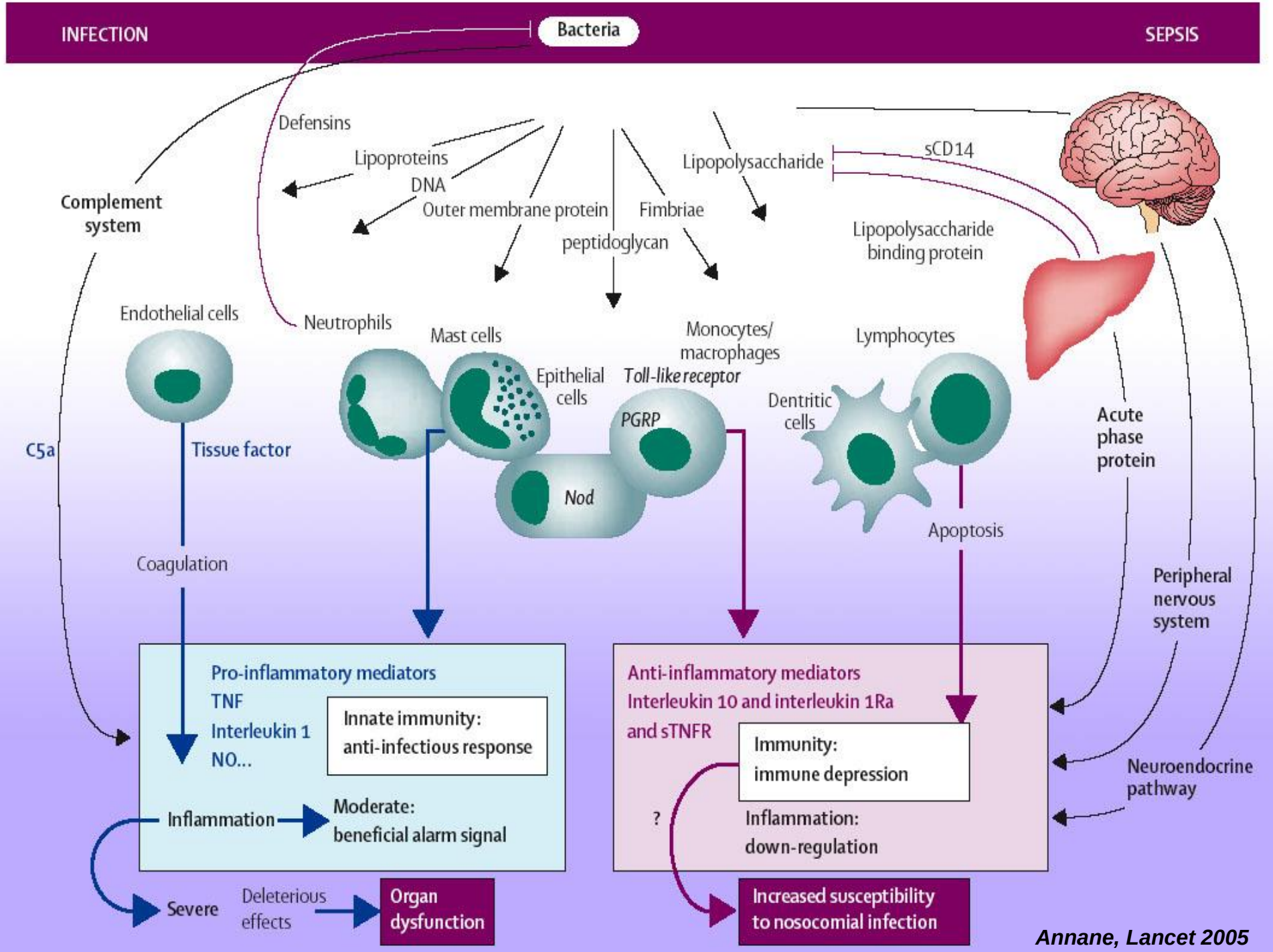
Ajit P. Limaye, MD
Katharine A. Kirby, MSc
Gordon D. Rubenfeld, MD
Wendy M. Leisenring, ScD
Eileen M. Bulger, MD
Margaret J. Neff, MD
Nicole S. Gibran, MD
Meei-Li Huang, PhD
Tracy K. Santo Hayes, BSc
Lawrence Corey, MD
Michael Boeckh, MD



JAMA® 2008;300(4):413-422



Annane, Lancet 2005

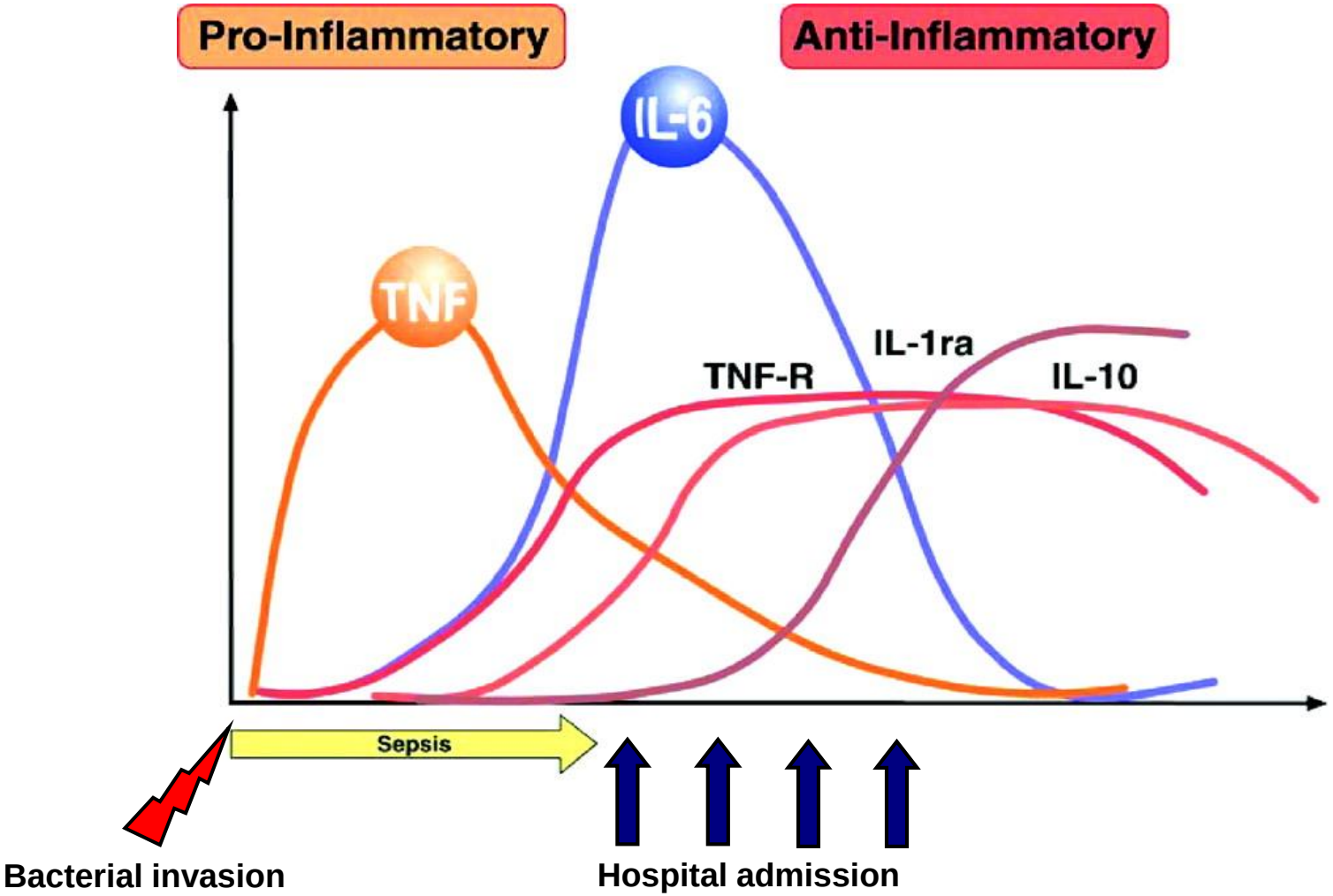


Annane, Lancet 2005

Sepsis-associated immunopathy

- **Synonymes:**
  - **« immuno-paralysie »**
  - **« immuno-dysfonction »**
  - **« immunodepression post-infectieuse »**
- **Connue depuis le milieu des années 90**
- **Complexe comme le suggère le phénotype des patients:**
  - **susceptibilité infectieuse multiple**
  - **déficit des fonctions lymphocytaires**
  - **déficit des fonctions phagocytaires…**

Dynamique de la réponse cytokinique au cours du sepsis



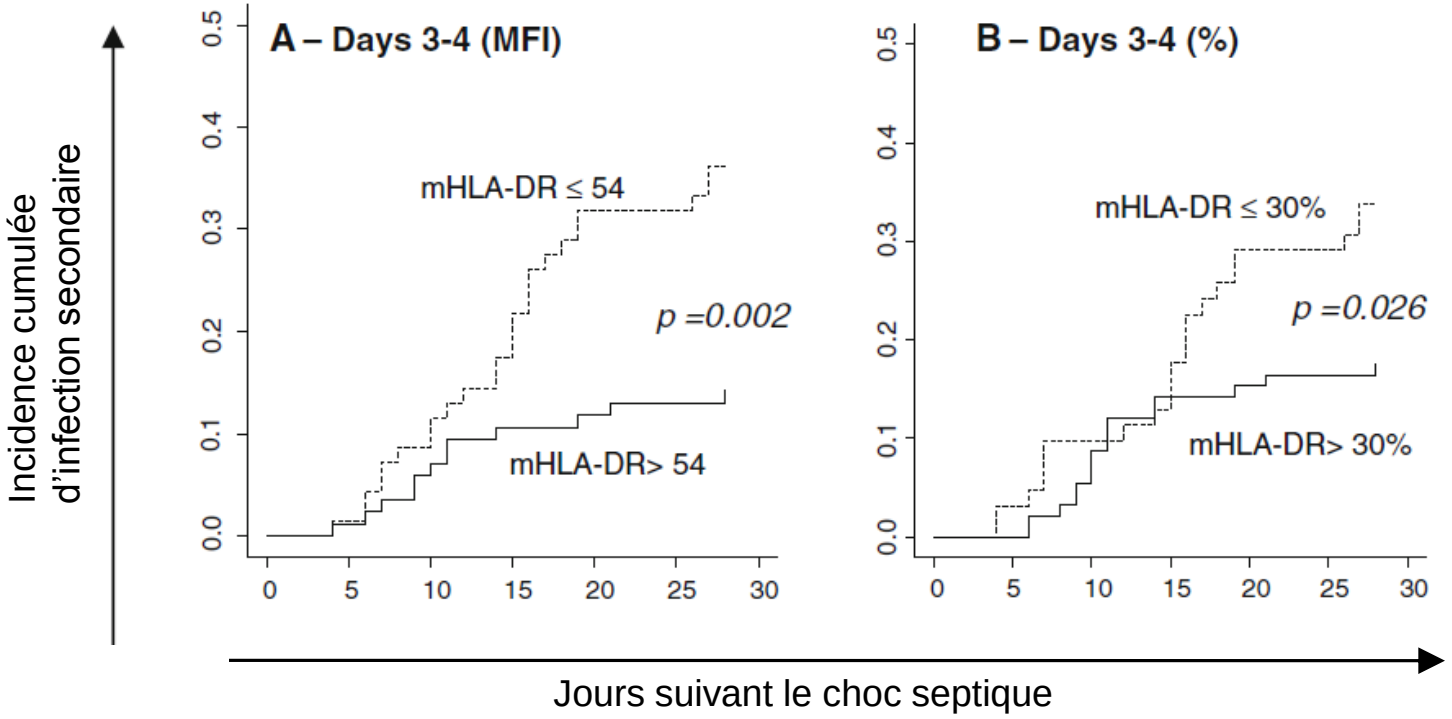
Adapté de Pedersen BK & Febbraio MA (2008). Physiol Rev 88, 1379–1406

Sepsis-induced immune dysfunctions

Immune dysfunctions	Mortality	ICU-acquired infections
Monocyte deactivation	++	++
Depletion of dendritic cells	+	+
Expansion of myeloid suppressor cells	+	+
Lymphopenia	+	+/-
Increase in Tregs	+	+
Depletion in MAIT cells		+
Decreased diversity of T-cell repertoire	+	+
Overexpression of inhibitory molecules	+	+
Reactivation of latent viruses	+	+

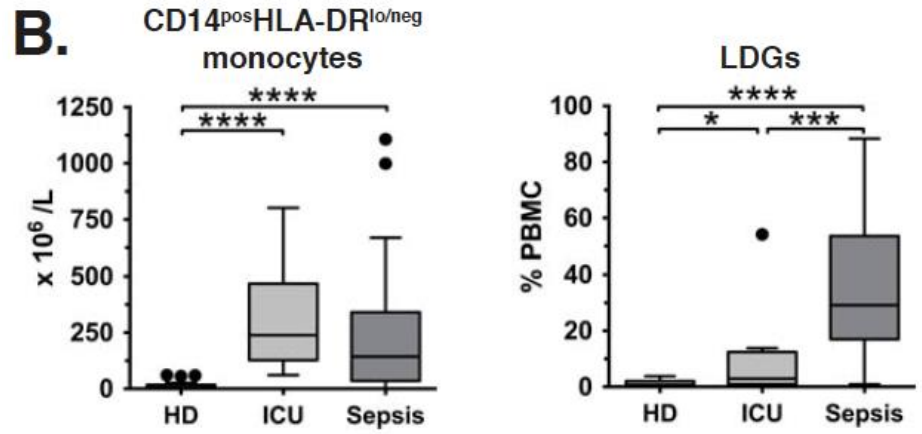
Caroline Landelle
Alain Lepape
Nicolas Voirin
Eve Tognet
Fabienne Venet
Julien Bohé
Philippe Vanhems
Guillaume Monneret

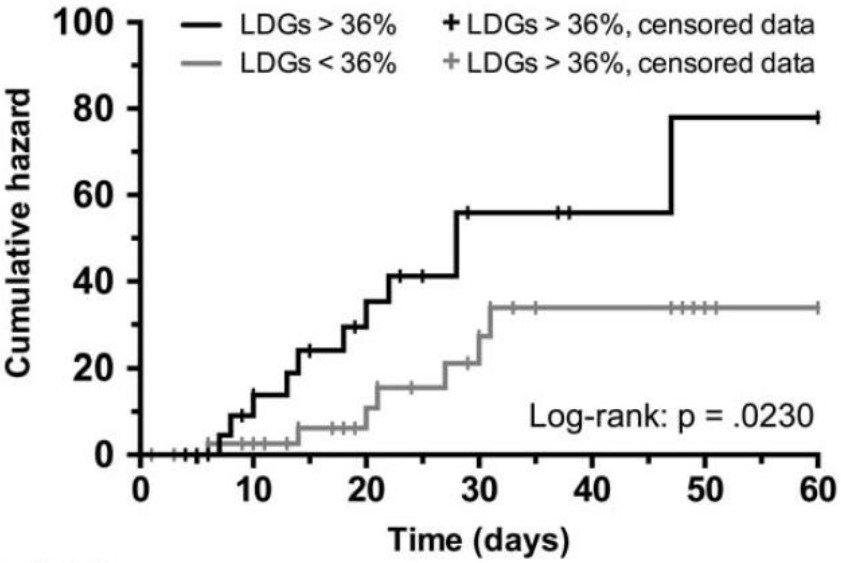
Low monocyte human leukocyte antigen-DR is independently associated with nosocomial infections after septic shock

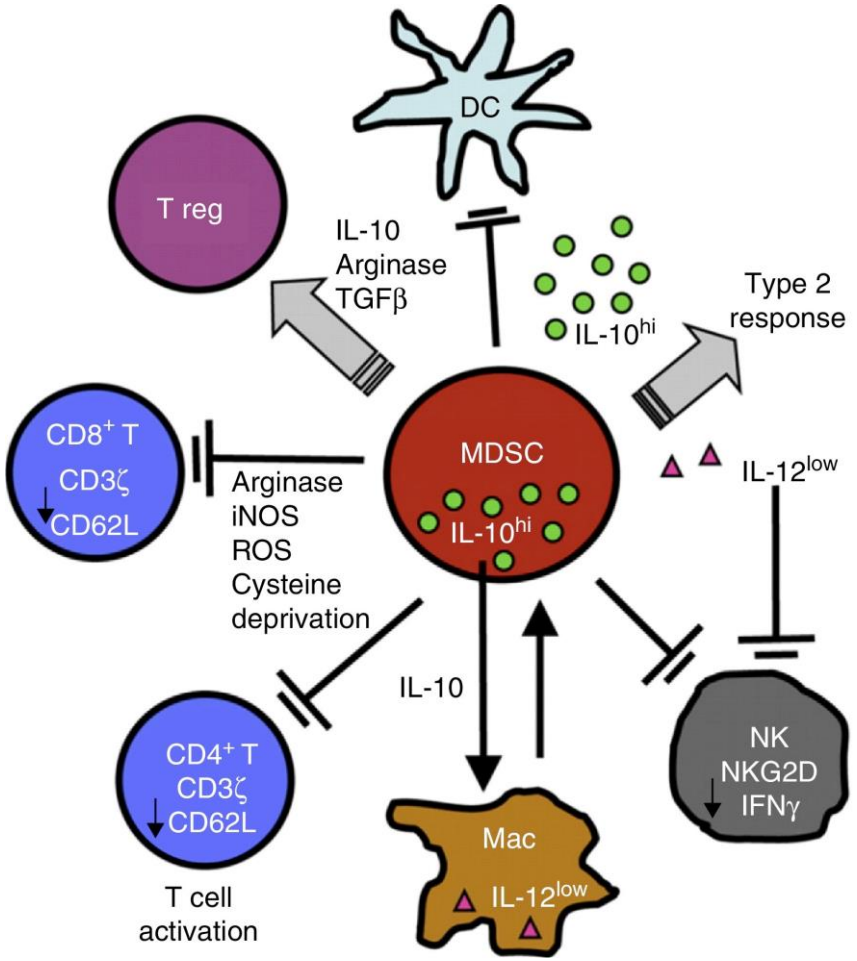


Intensive Care Med 2010

Expansion of MDSCs



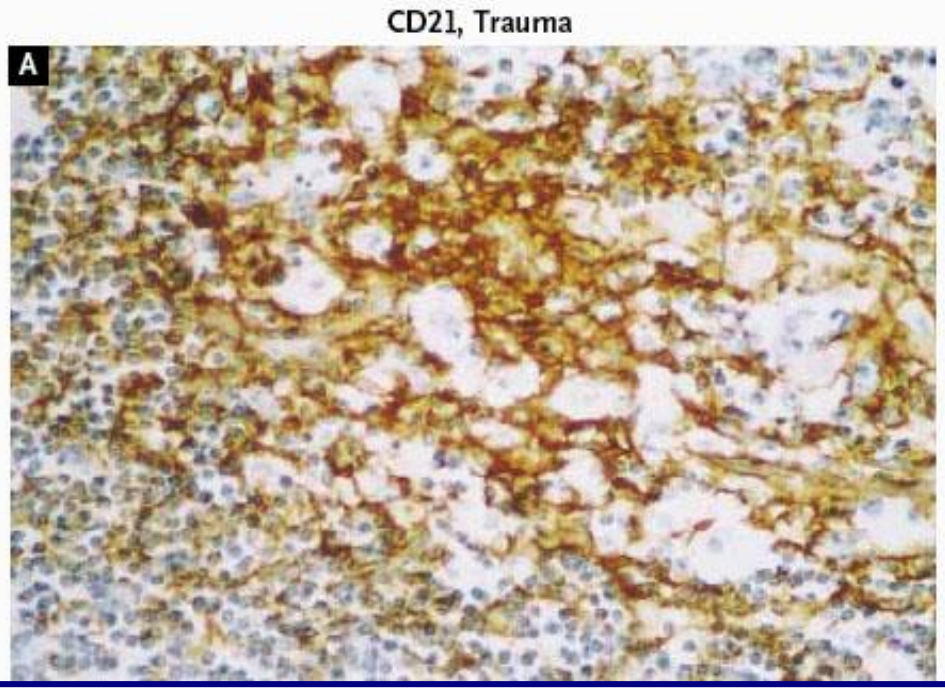


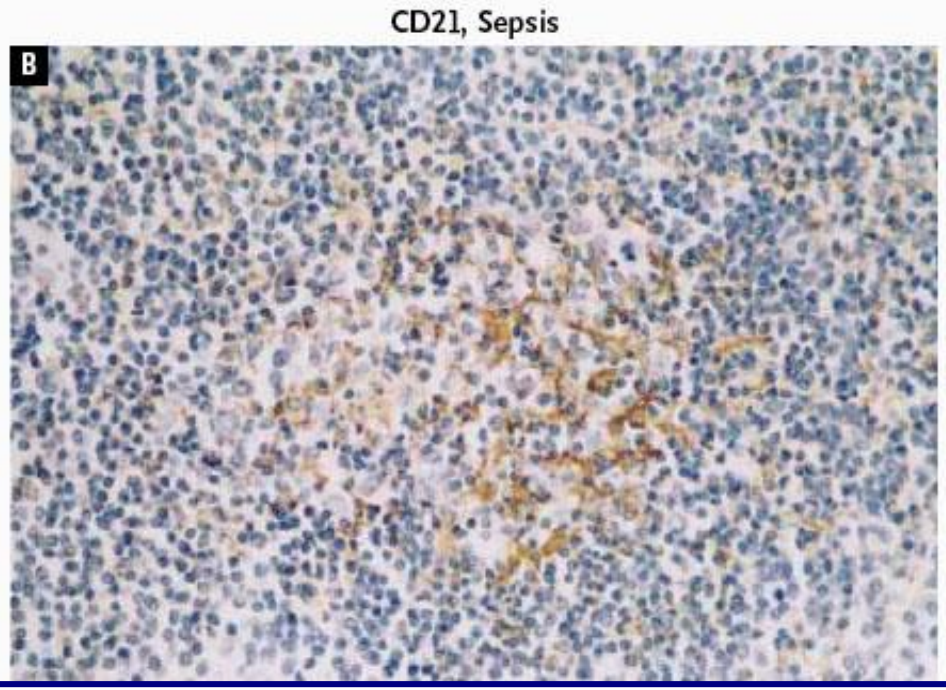


Uhel et al. AJRCCM 2017

Scrimini Arch Bronconeumol 2016

Apoptose des Cellules Dendritiques



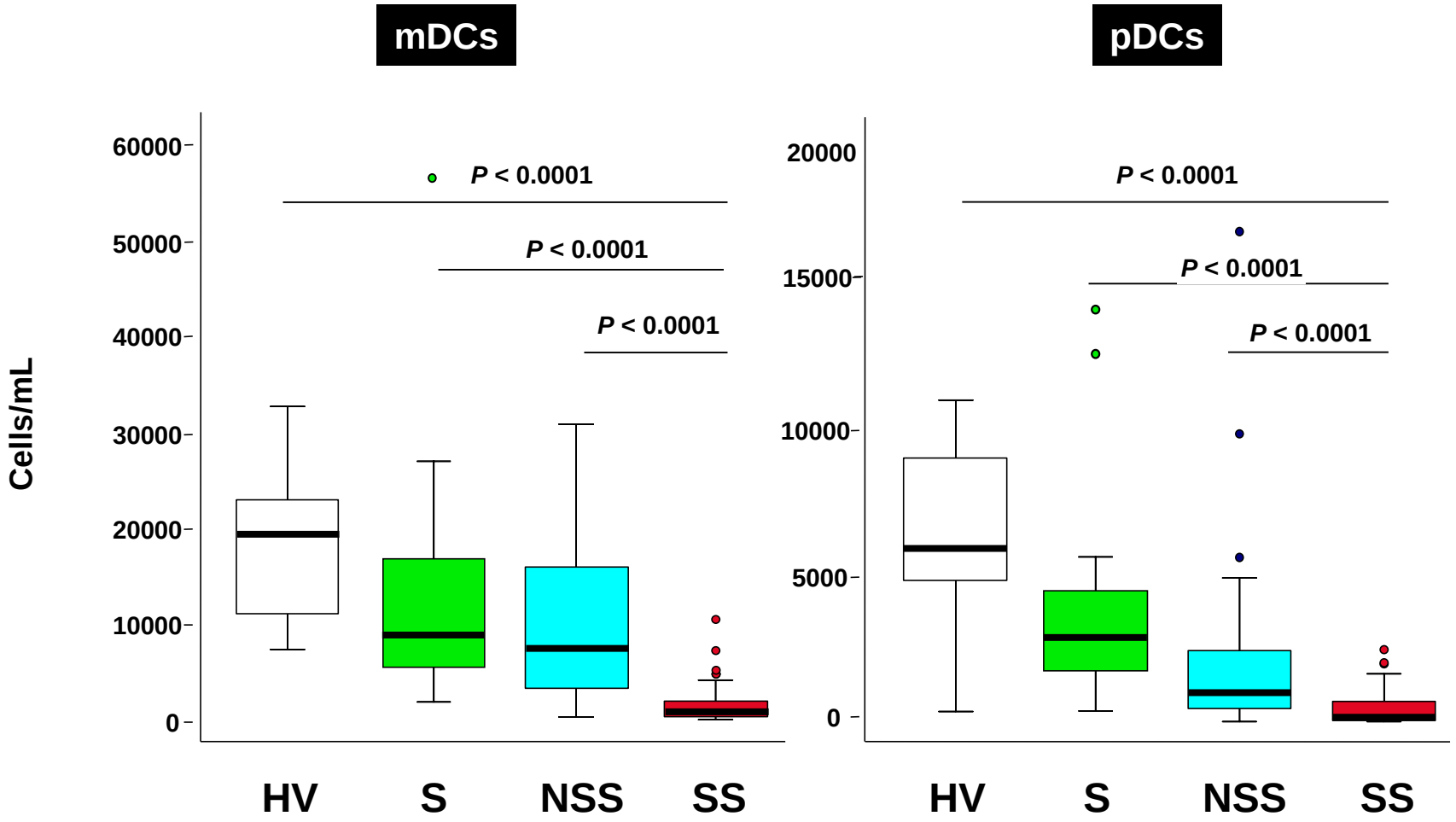


Autopsies: n= 26

Splénectomies: n= 3

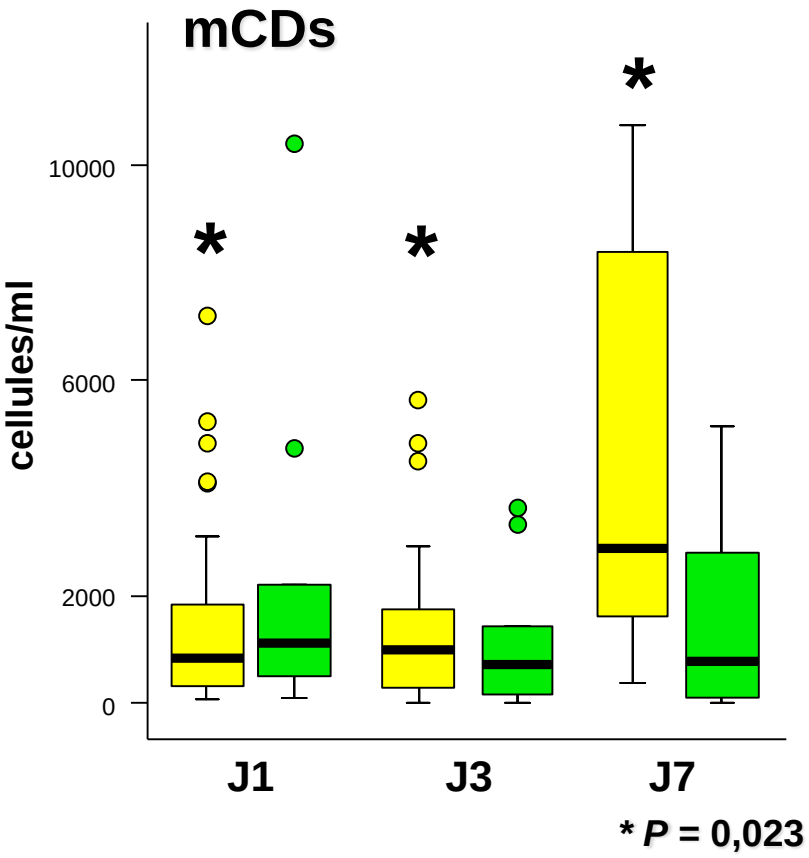
Hotchkiss J Immunol 2002

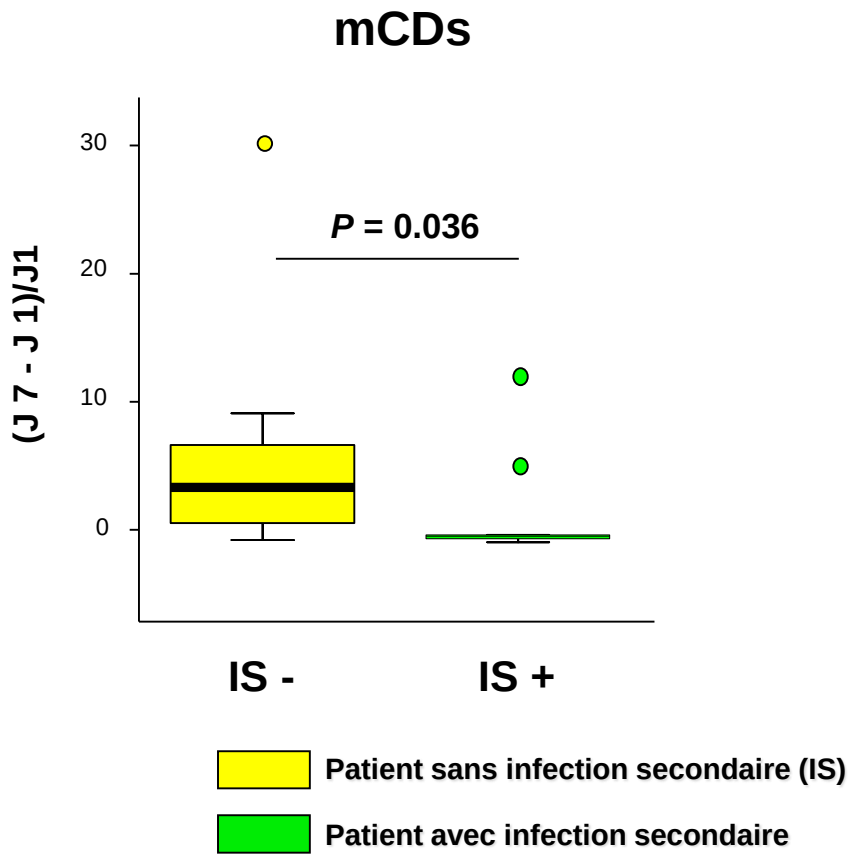
Numération des CDs circulantes à J1



Grimaldi D Intensive Care Med 2011

Evolution des CDs et survenue d'une infection secondaire





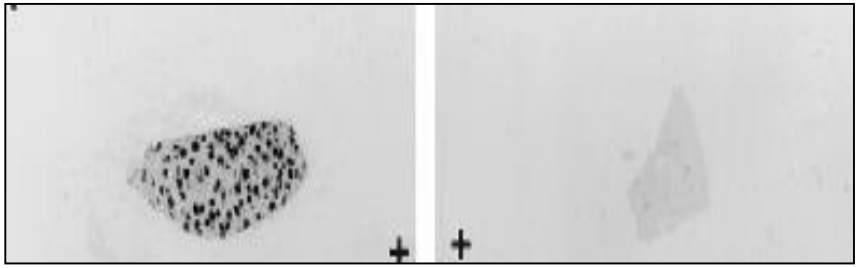
Baisse des mCDs associée avec infection secondaire : OR 22 (2.53-191) *P* = 0.005

Grimaldi D Intensive Care Med 2011

Apoptose des lymphocytes T et B

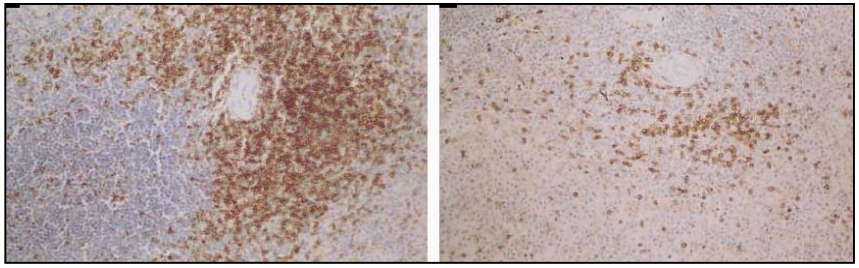
B cell (CD20)

Trauma **Sepsis**

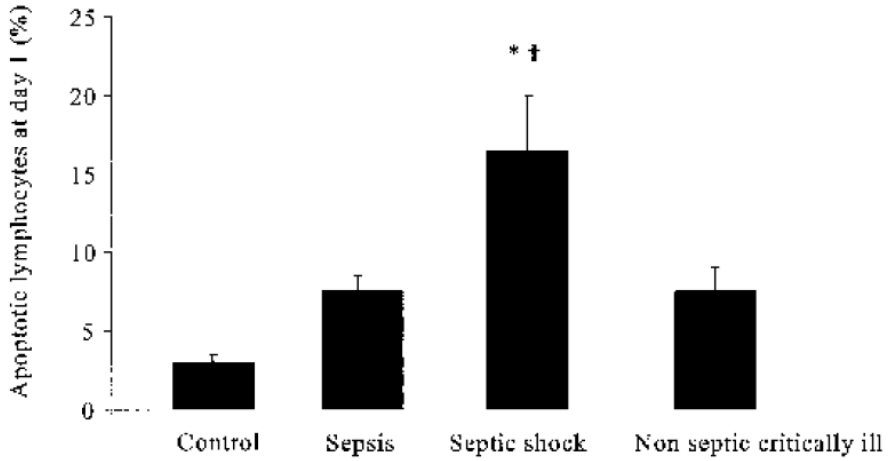


T cell (CD4)

Trauma **Sepsis**

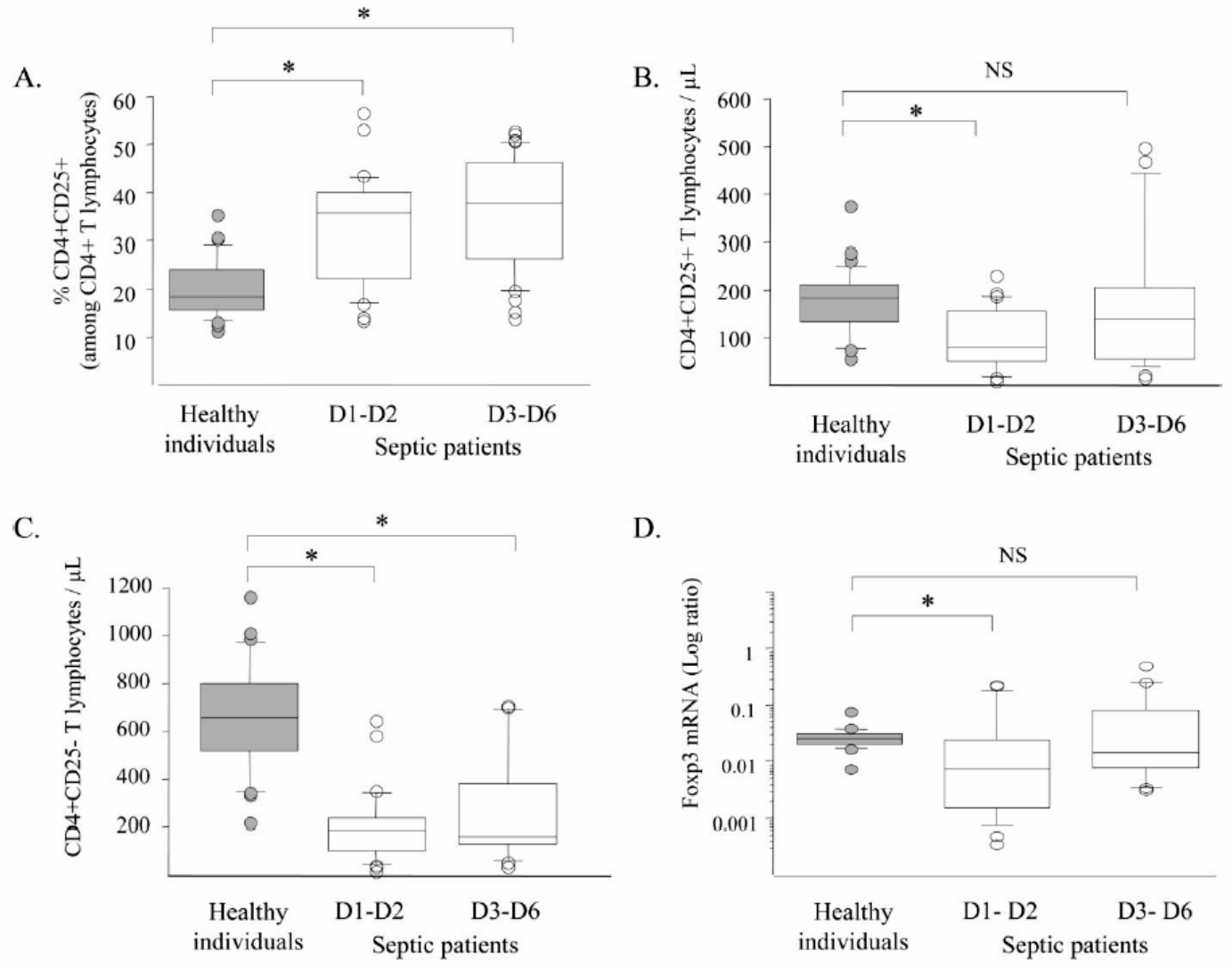


Hotchkiss, J Immunol 2001



Le Tulzo, Shock 2002

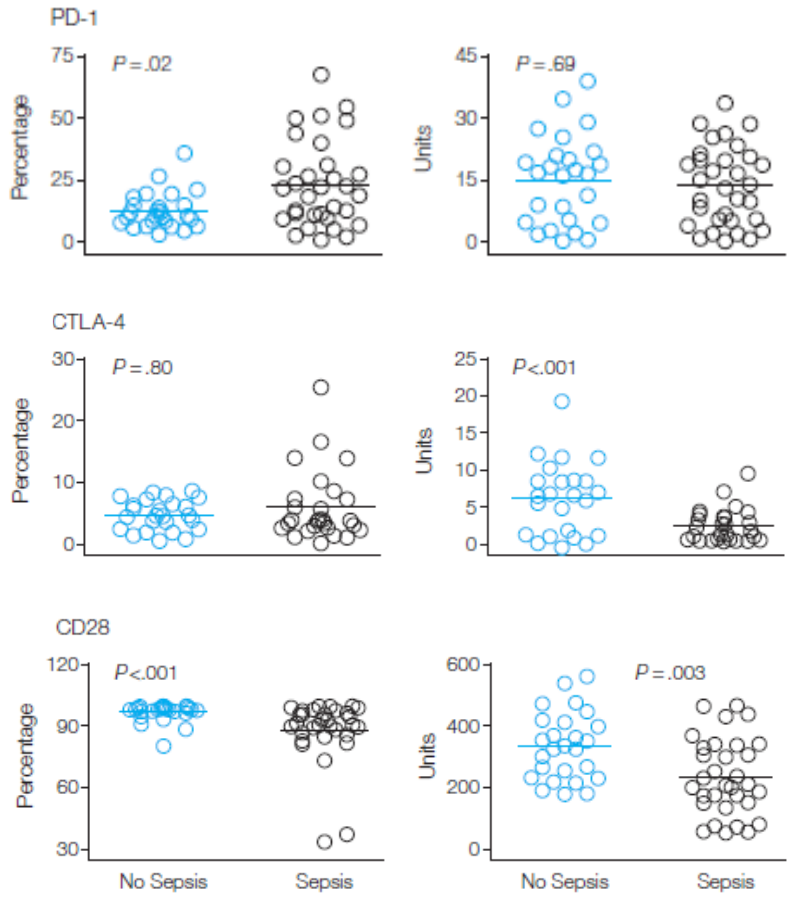
Augmentation relative des T regs



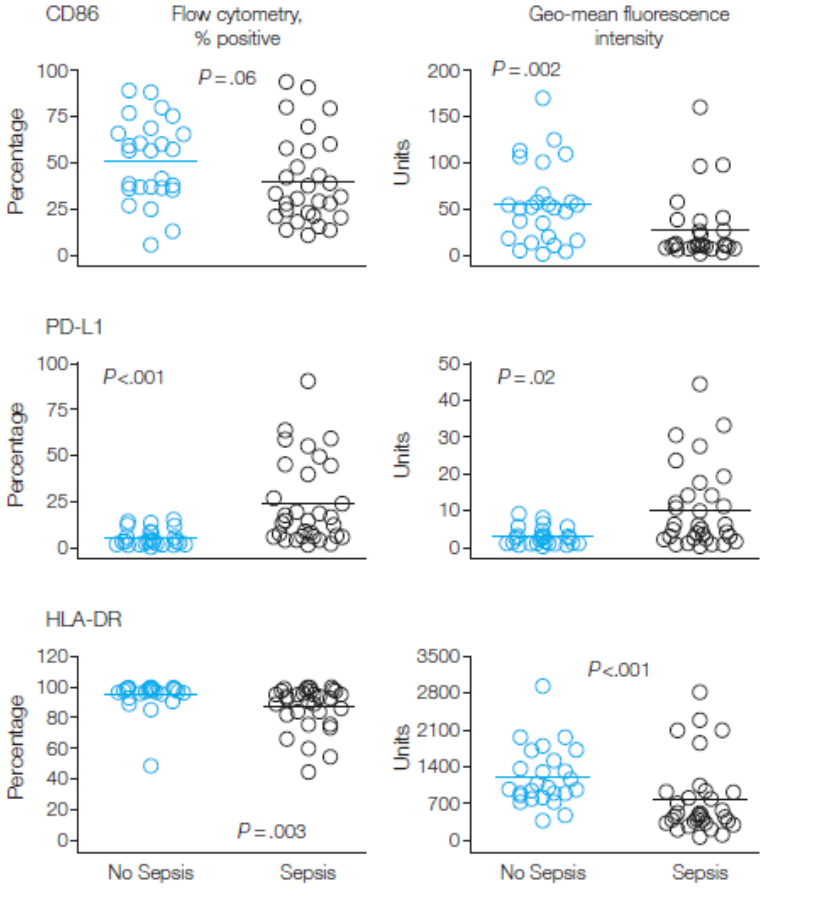
Venet, Crit Care Med 2004

Expression splénique de molécules de co-stimulation inhibitrices chez des patients décédés

LT CD4

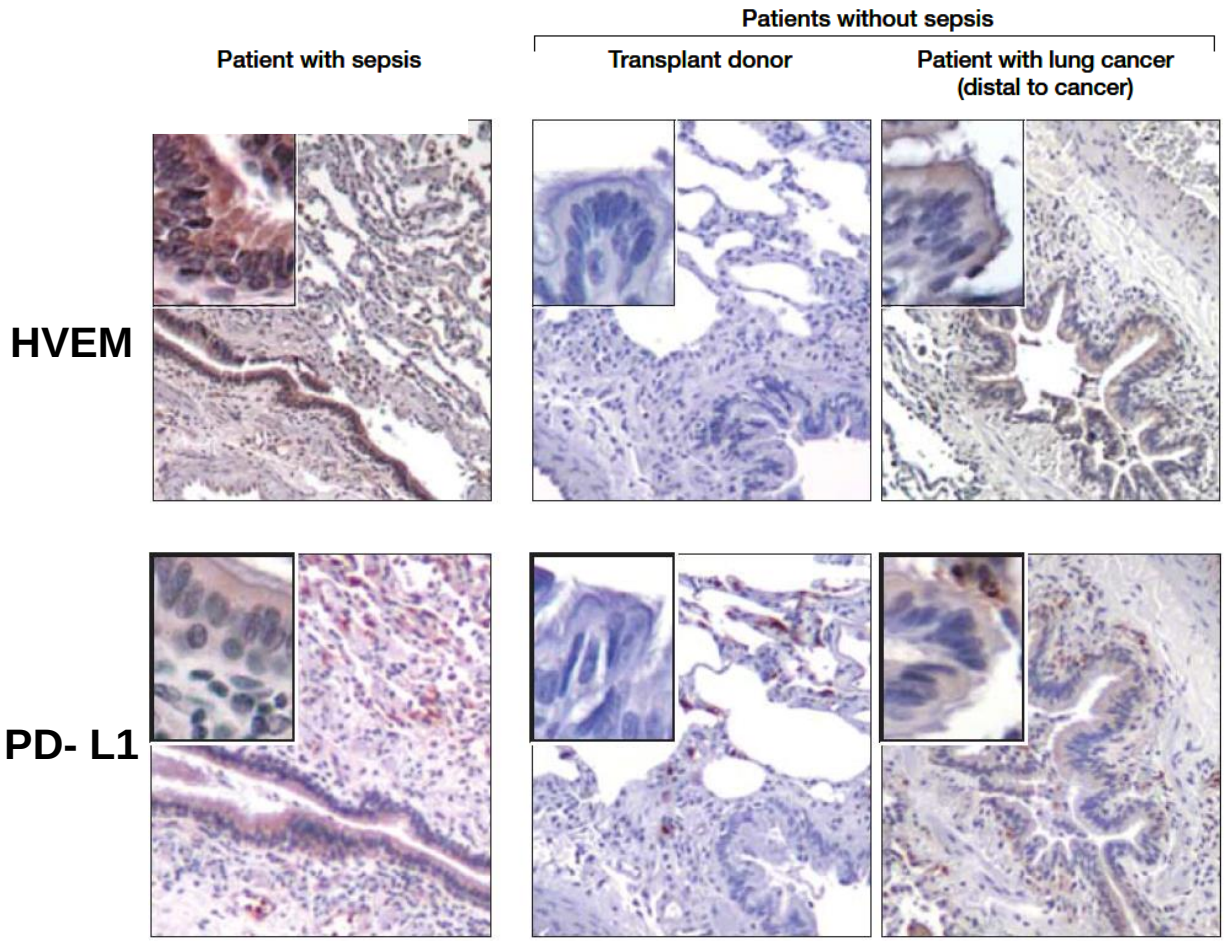


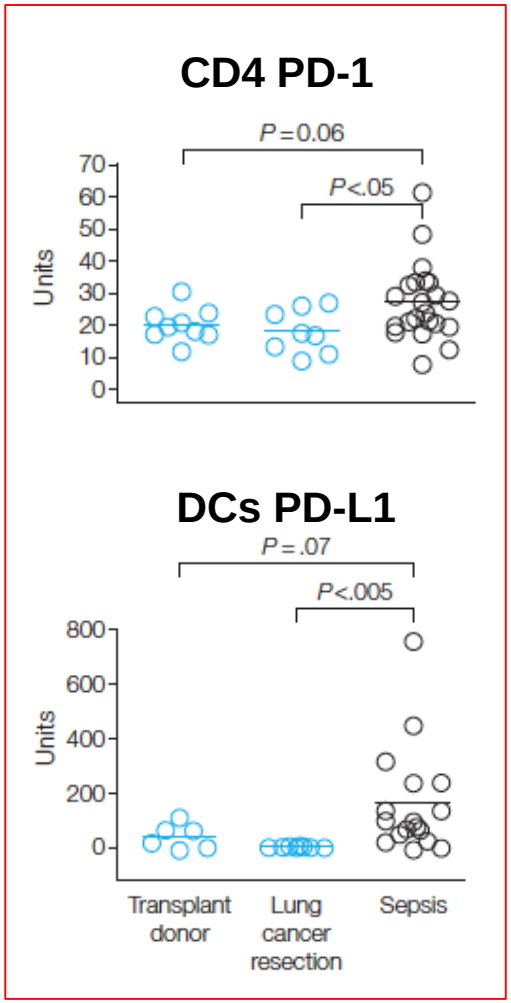
CPA



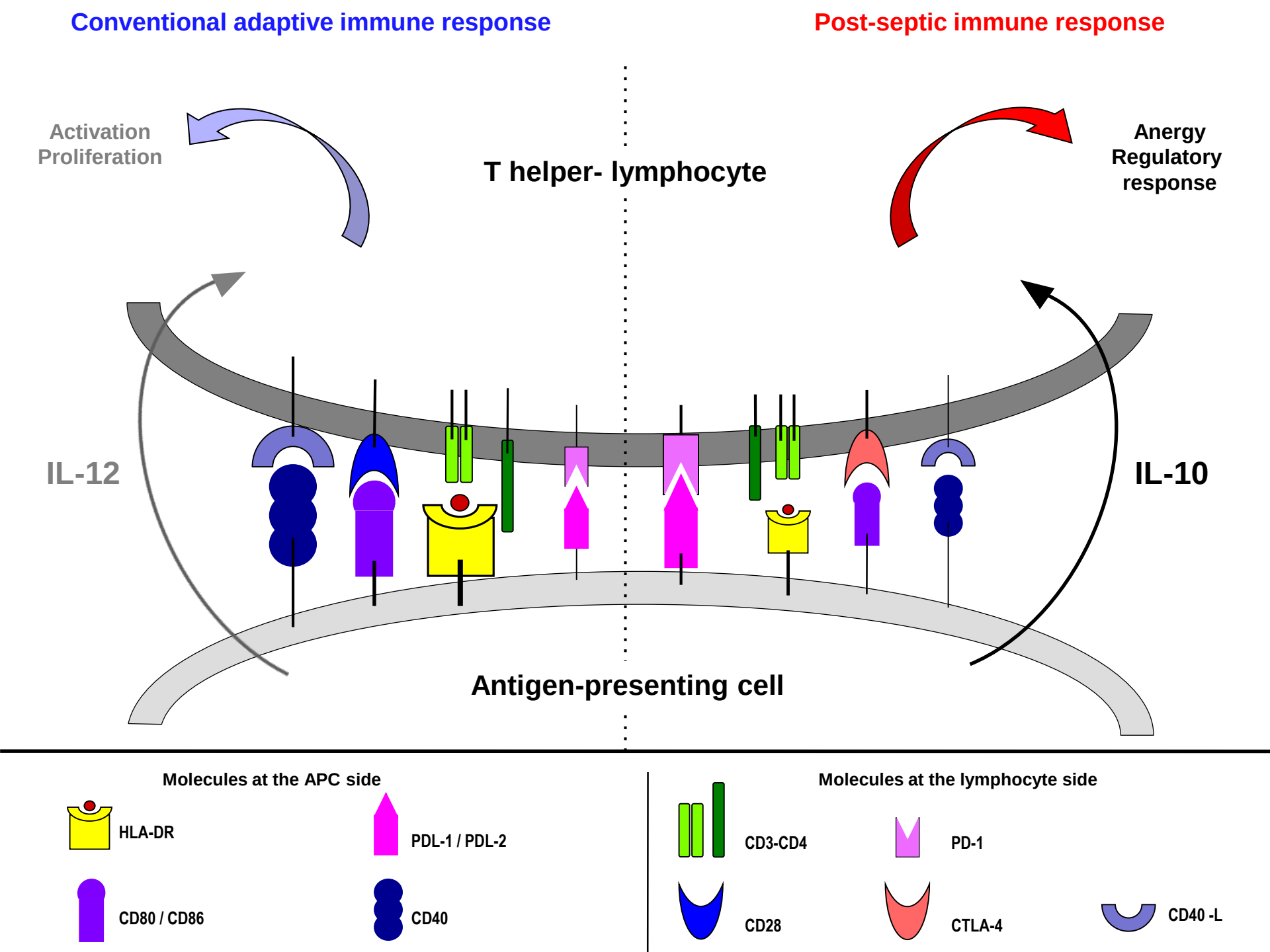
Boomer et al. JAMA 2011

Expression pulmonaire de molécules de co-stimulation inhibitrices chez des patients décédés





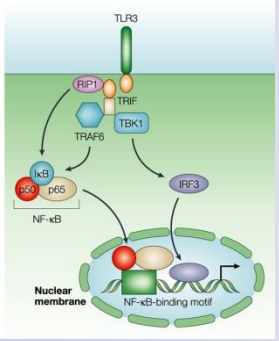
Boomer et al. JAMA 2011

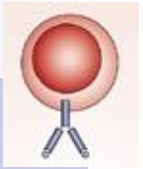

Conventional adaptive immune response
Post-septic immune response
Activation
Proliferation
T helper- lymphocyte
Anergy
Regulatory
response
IL-12
IL-10
Antigen-presenting cell
Molecules at the APC side
HLA-DR
PDL-1 / PDL-2
CD80 / CD86
CD40
Molecules at the lymphocyte side
CD3-CD4
PD-1
CD28
CTLA-4
CD40 -L

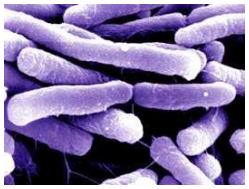
Immune function workshop

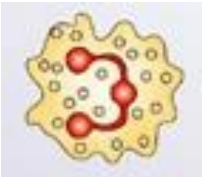
- No previous infection
- No familial history
- Normal leukocyte count, no neutropenia
- Moderate lymphopenia 0.66 G/L including 0.43 CD4+ and 0.07 CD8+ cells

	Control (N=8) Mean (SD)	Patient
HLA-DR mono MFI	11.4 (2.8)	2.88
CD86 mono-MFI	5.26 (0.74)	1.60
CD86 mono-%	99.8 (0.23)	62.0
PD-1 CD4 %	9.30 (3.00)	22.28
PD-1 CD8 %	6.02 (4.4)	9.76
#lymphocytes	NM	0.661
#CD4	NM	0.430
#CD8	NM	0.068

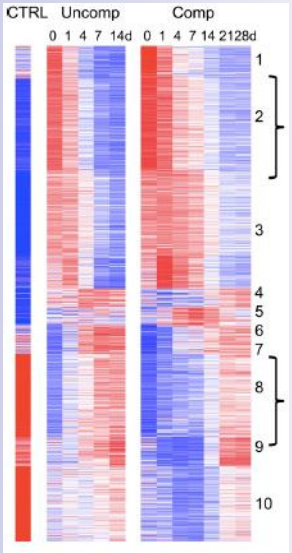


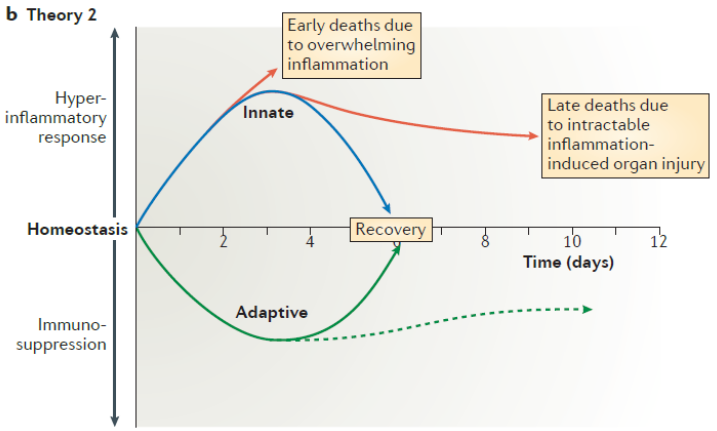




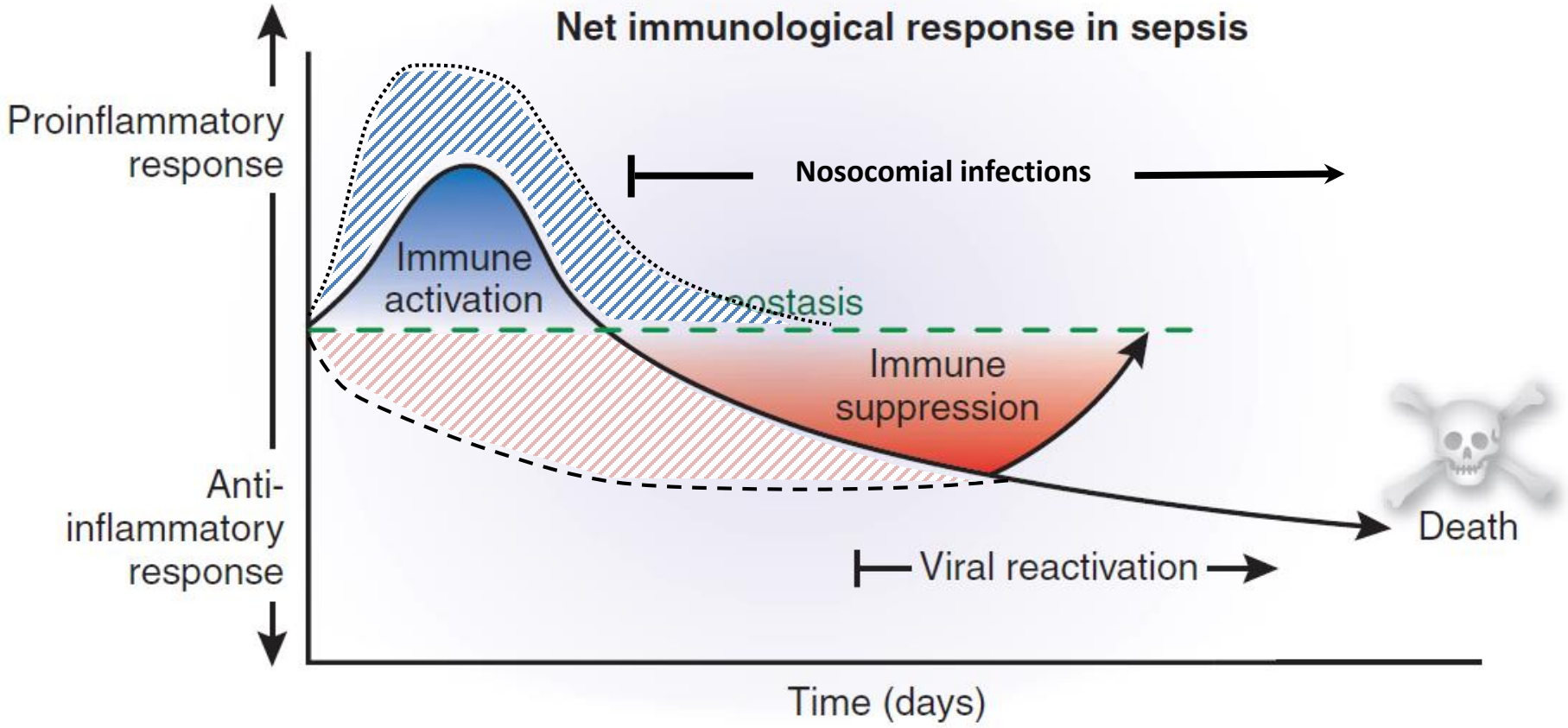


Immunodépression ou dysrégulation ?



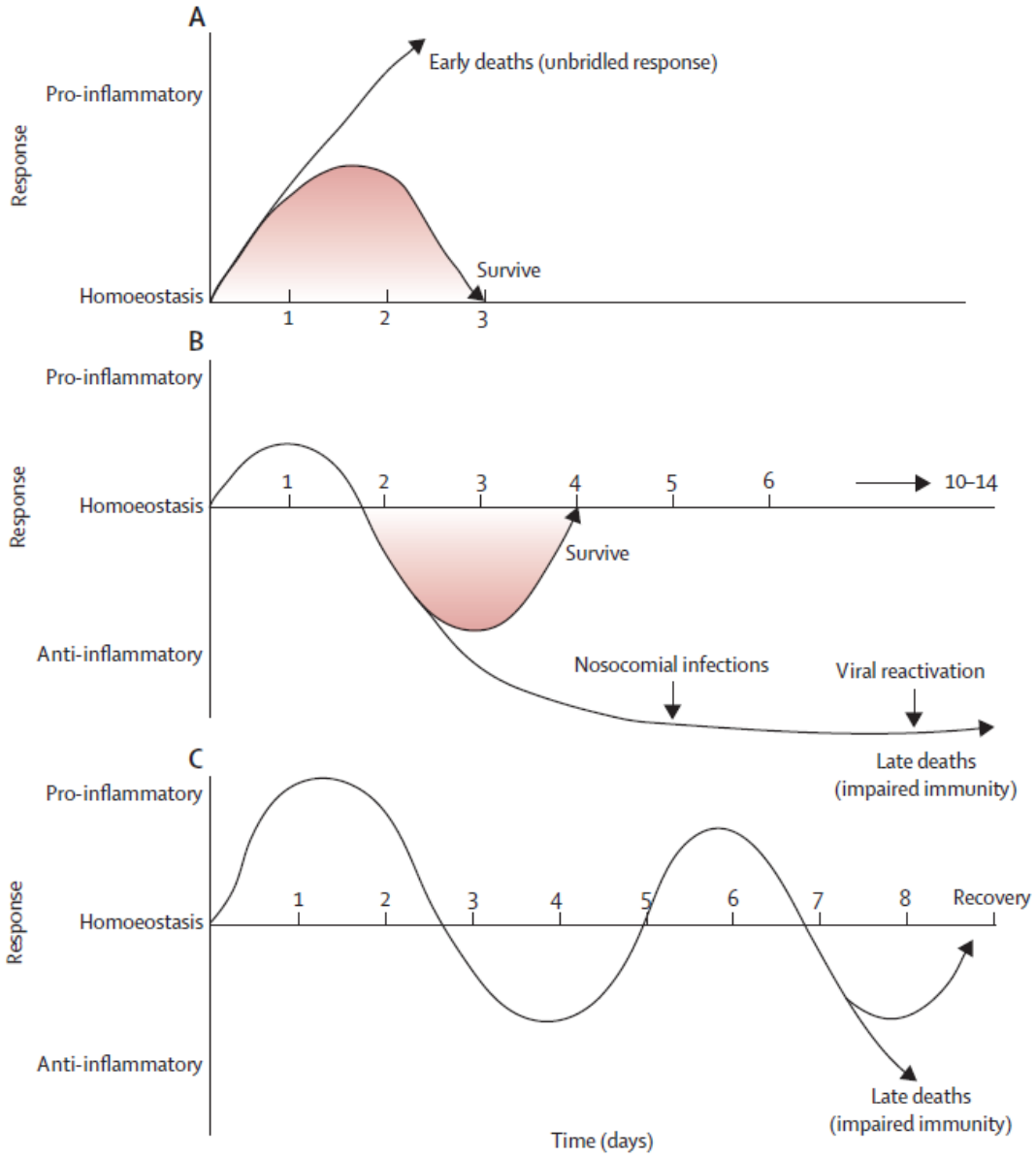


The sepsis seesaw



adapted from Hotchkiss et al., Nat Med 2009

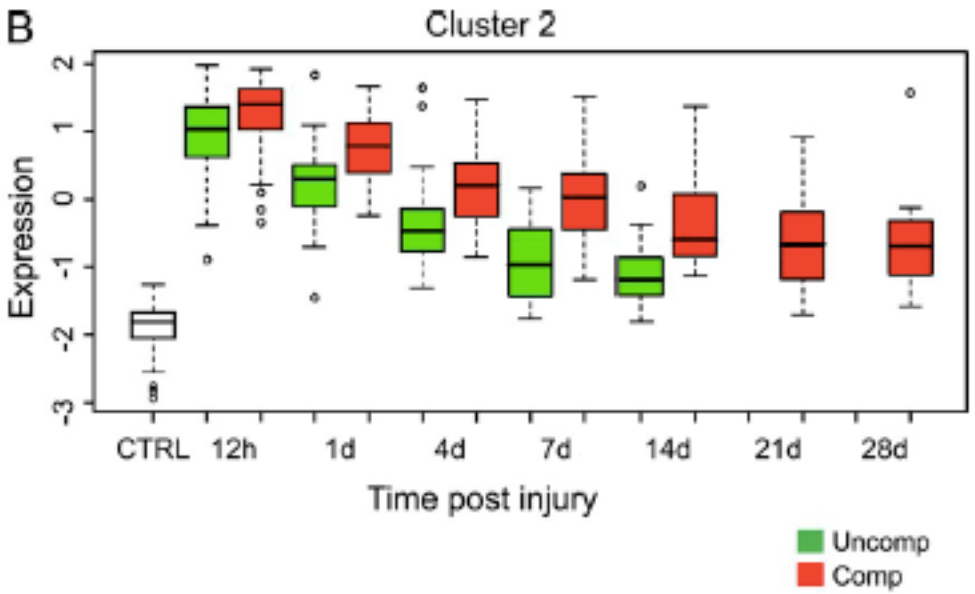
Are the ICU patients permanently immunocompromized ?

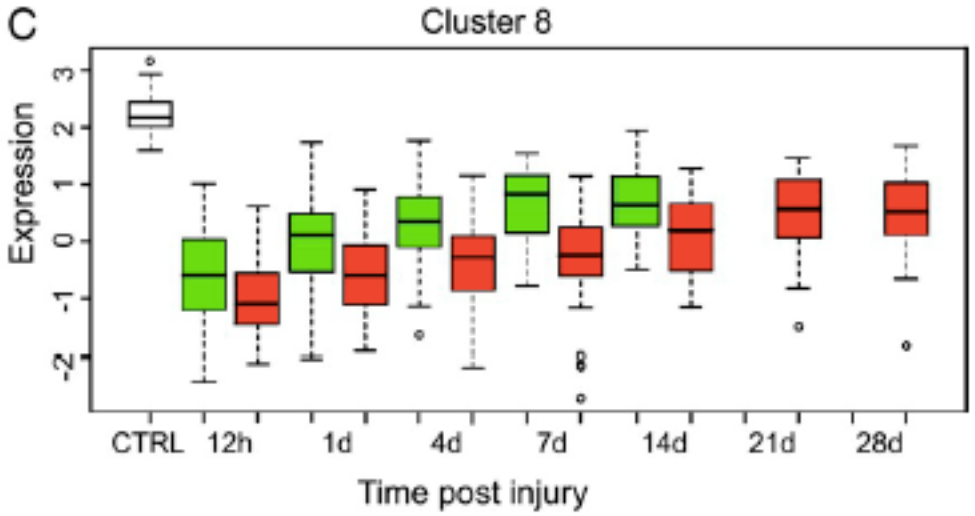


Hotchkiss et al. Lancet Infect Dis 2013

Dysrégulation ?

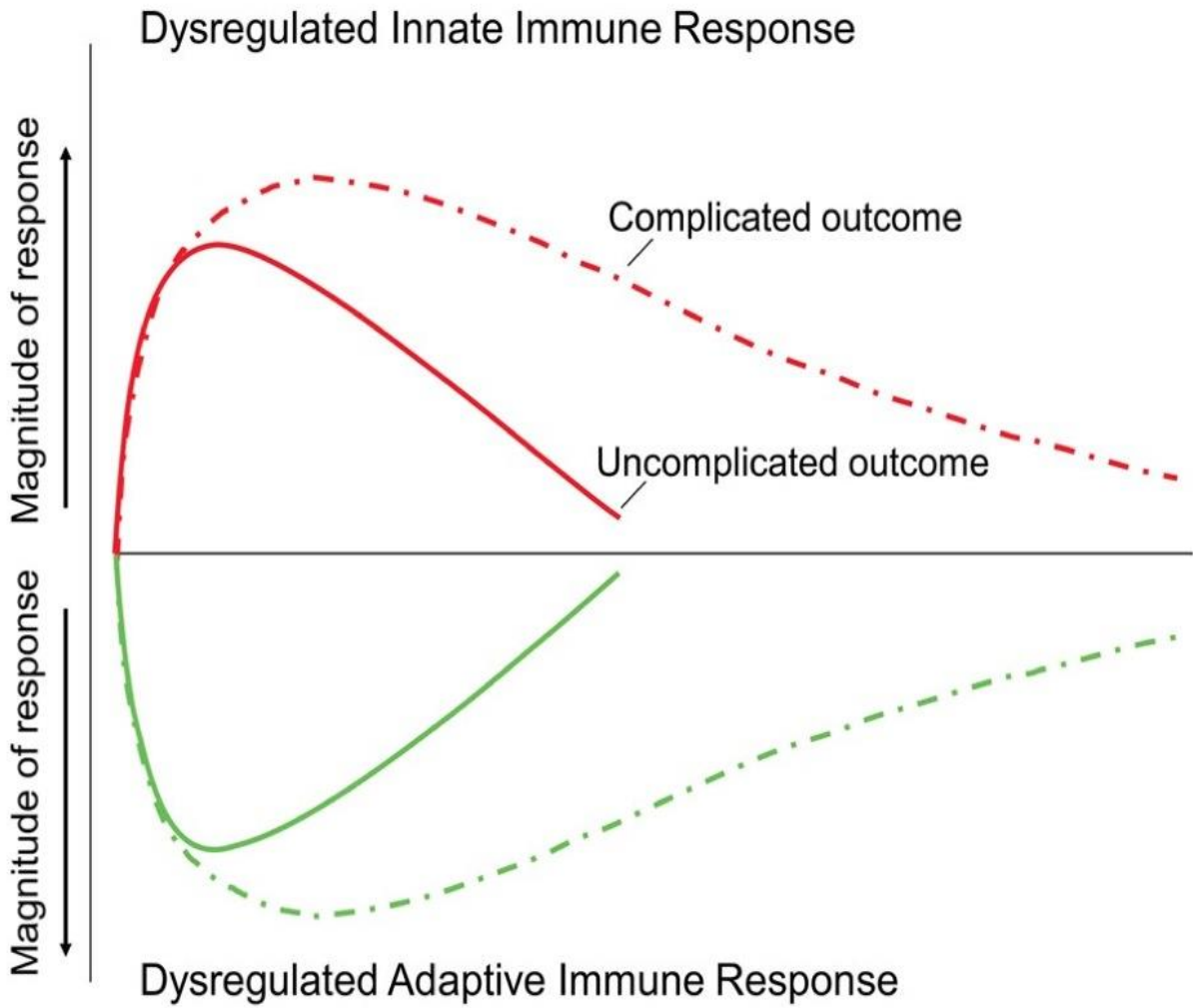
- **Coexistence de gènes activés et réppримés**
- **Persistance de profils pro-inflammatoires au sein des cellules de l'immunité innée ?**





Xiao et al. J Exp Med 2011

Théorie alternative … ou complémentaire

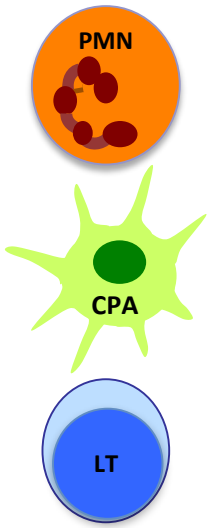


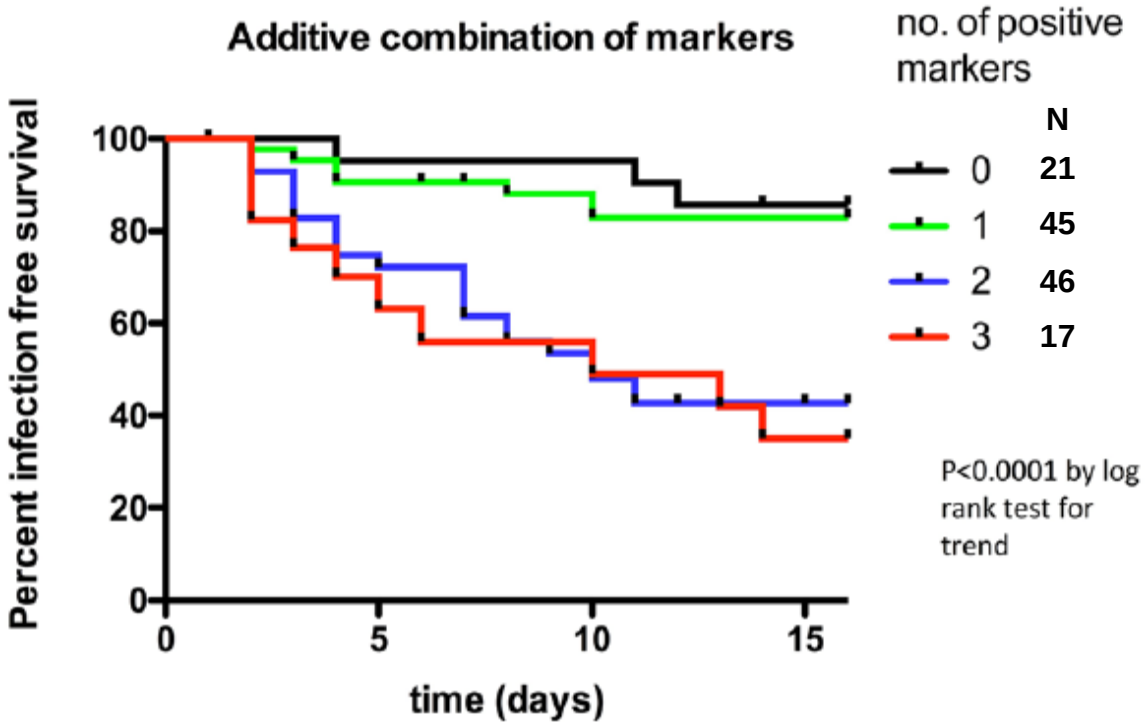
Xiao et al. J Exp Med 2011

Cumulative effects of immune dysfunctions ?

Multicentric UK study
138 patients
Immune assays/ 2d
3 dysfunctions assessed

Marker	Cut-off	OR
CD88	≤ 9609	2.18 (1.00–4.74)
Monocyte HLA-DR	≤ 2009	3.44 (1.58–7.47)
T_{regs} as % of CD4 cells	≥ 12.12	2.41 (1.14–5.11)





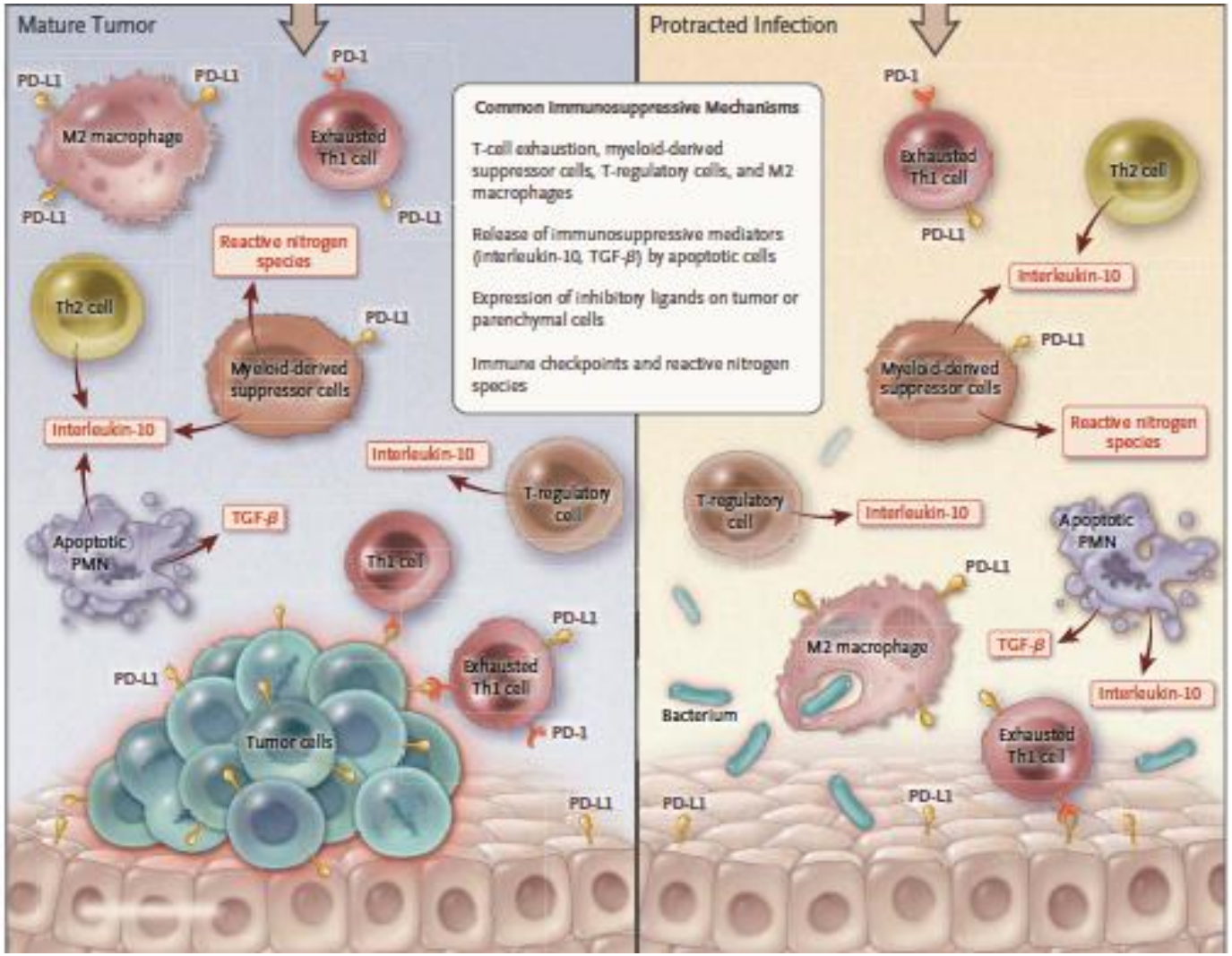
Morris et al. Intensive Care Med 2018

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Parallels between Cancer and Infectious Disease

Richard S. Hotchkiss, M.D., and Lyle L. Moldawer, Ph.D.



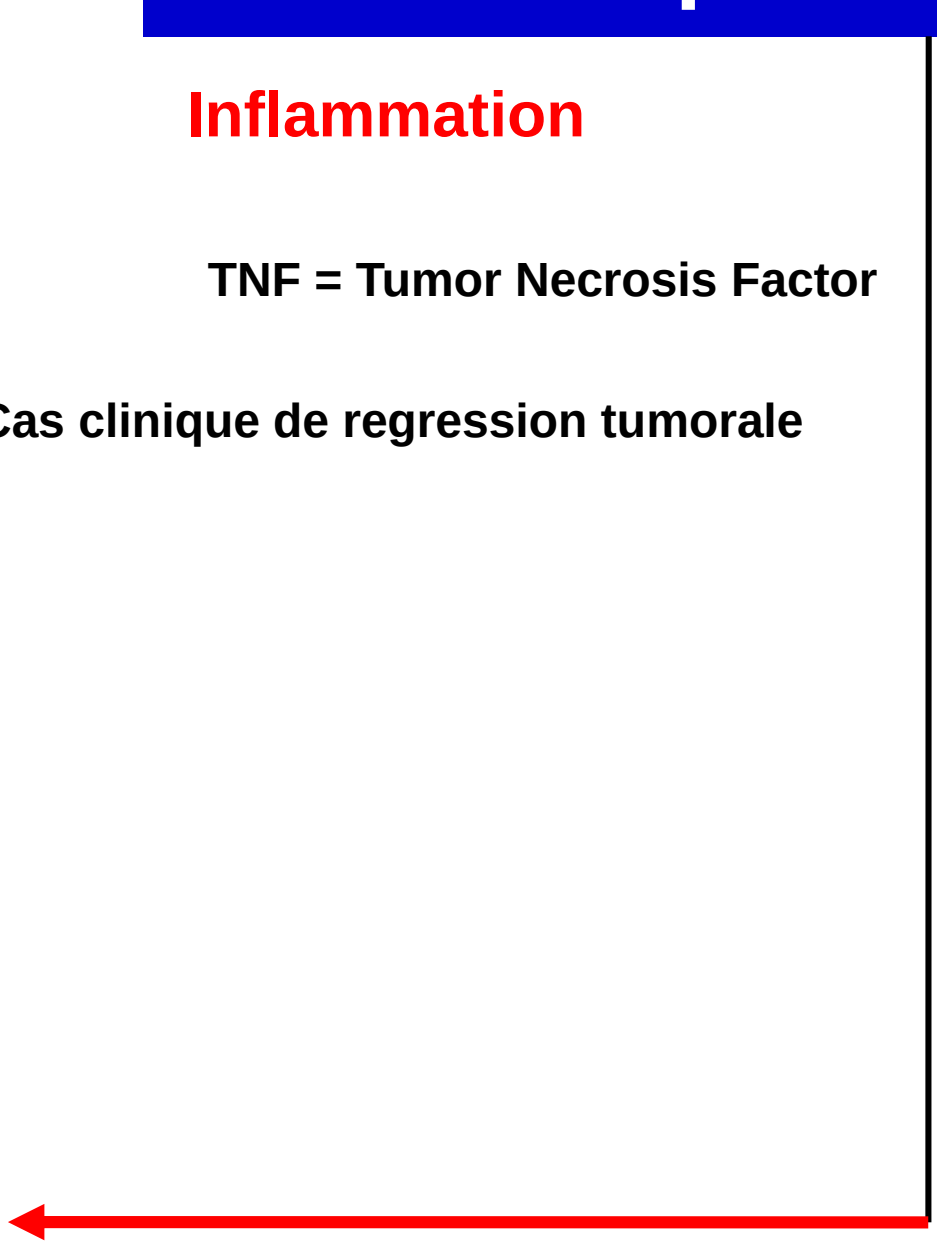
Hotchkiss & Moldawer New Engl J Med 2014

Sepsis & cancer

Inflammation

TNF = Tumor Necrosis Factor

Cas clinique de regression tumorale



immune balance

Sepsis & cancer

Inflammation

TNF = Tumor Necrosis Factor

Cas clinique de regression tumorale

Erysipèle pour traiter le sarcome
Coley W Ann Surg 1891

immune balance

Sepsis & cancer

Inflammation

TNF = Tumor Necrosis Factor

Cas clinique de regression tumorale

Erysipèle pour traiter le sarcome
Coley W Ann Surg 1891

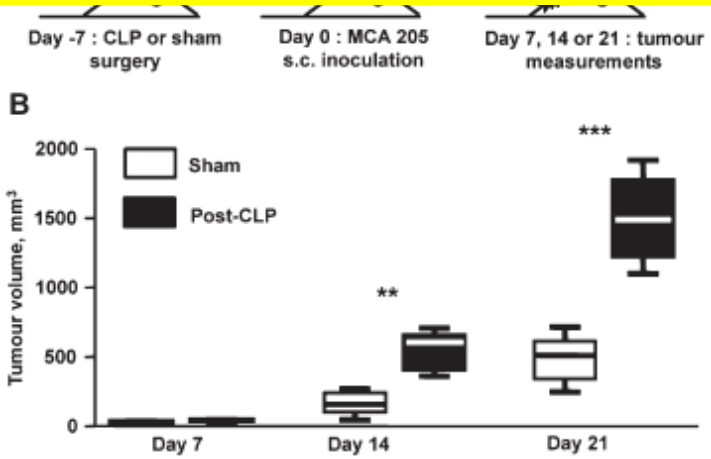
Immunosuppression

Données épidémio sepsis -> cancer

Données théoriques

Données expérimentales

Evidence clinique ?



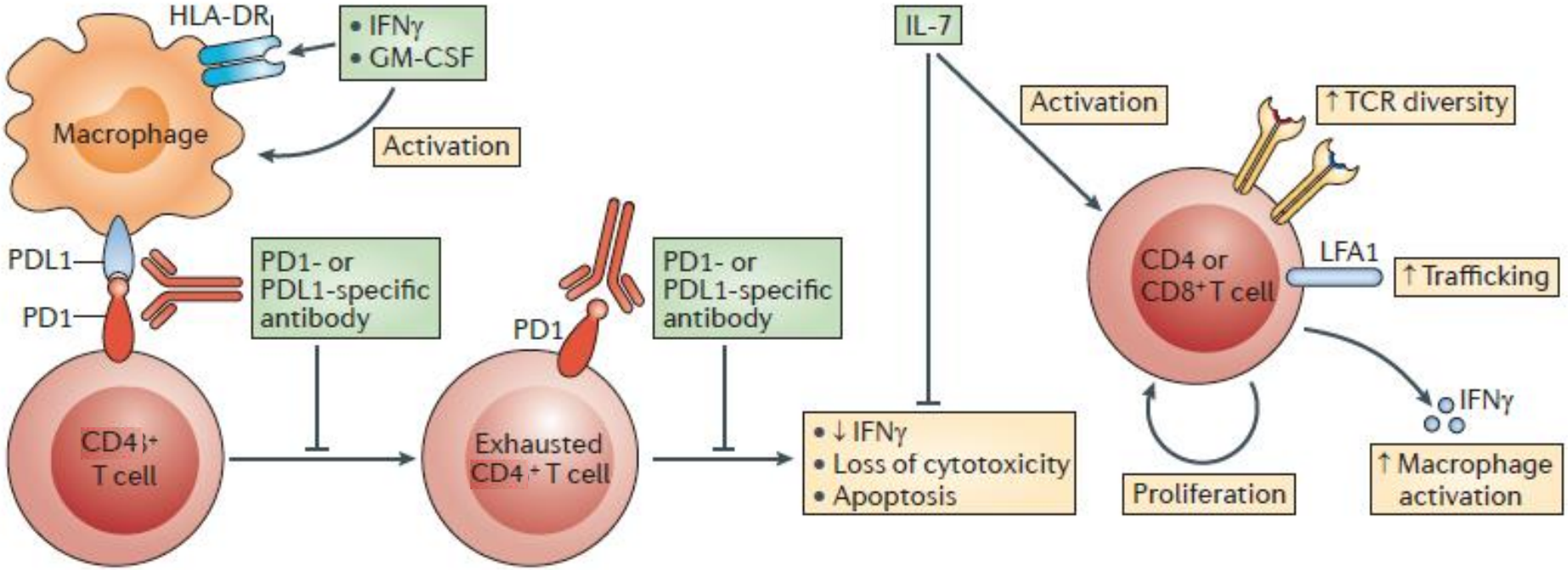
Llitjos et al. J Path 2016

immune balance

Questions non résolues

- Quelles altérations immunitaires chez quels patients ?
- Quels sont les facteurs de risque ?
  - D'acquisition – gravité (scores – choc)
  - De persistance
- Quel(s) marqueur(s) ?
- Susceptibilité spécifiques pour certains pathogènes ?
- Spécificité du sepsis ?
- Quelle durée ?
- Un traitement ?

Immunostimulant strategies during sepsis

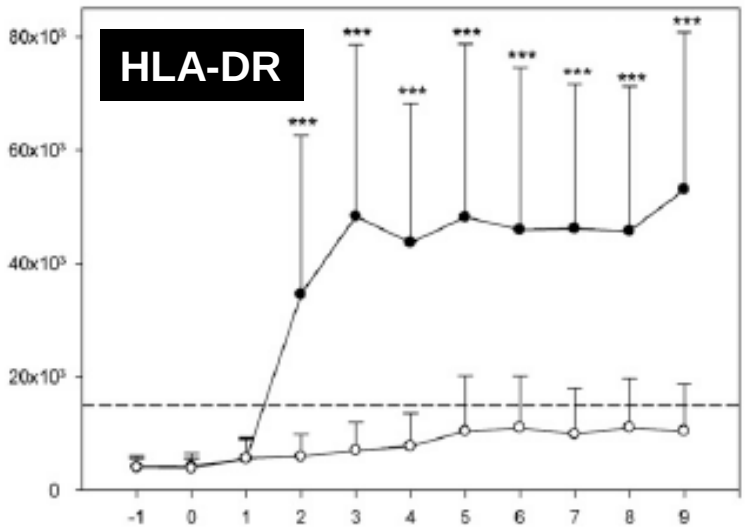


Hotchkiss , Monneret & Payen *Nat rev Immunol 2013*

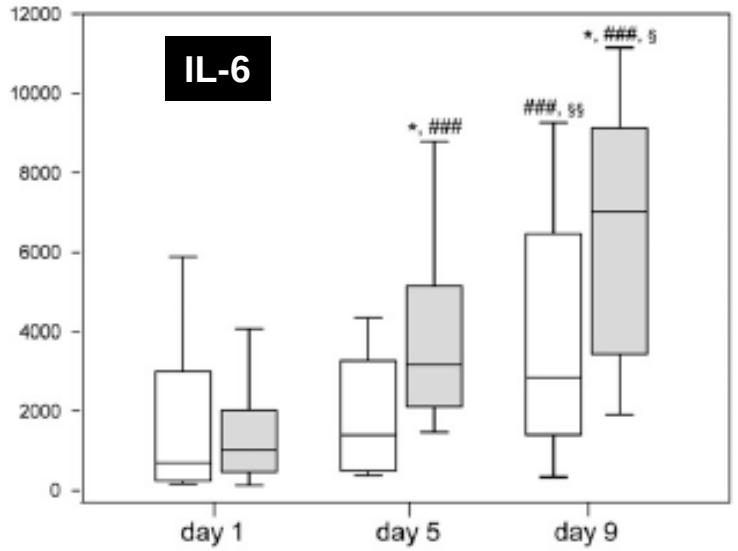
Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

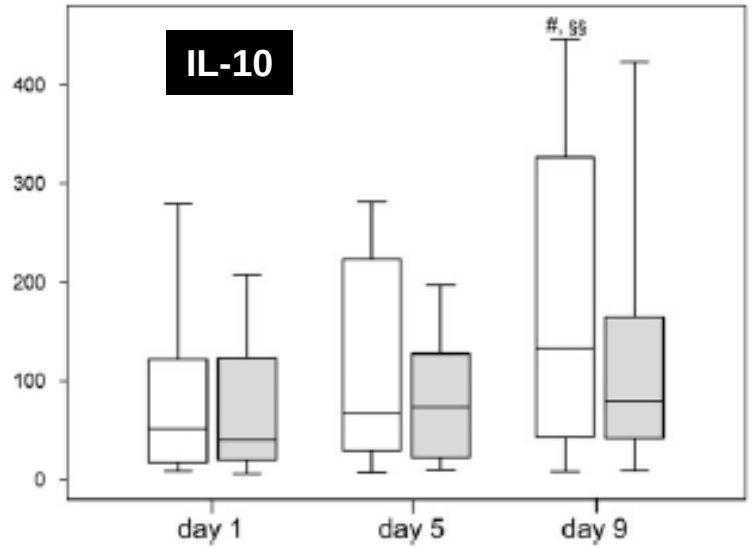
A Double-Blind, Randomized, Placebo-controlled Multicenter Trial

AMERICAN JOURNAL OF Respiratory and Critical Care Medicine



- **Phase II**
- **19 patients/group**
- **Similar mortality**
- **higher VFD in GM-CSF treated patients**

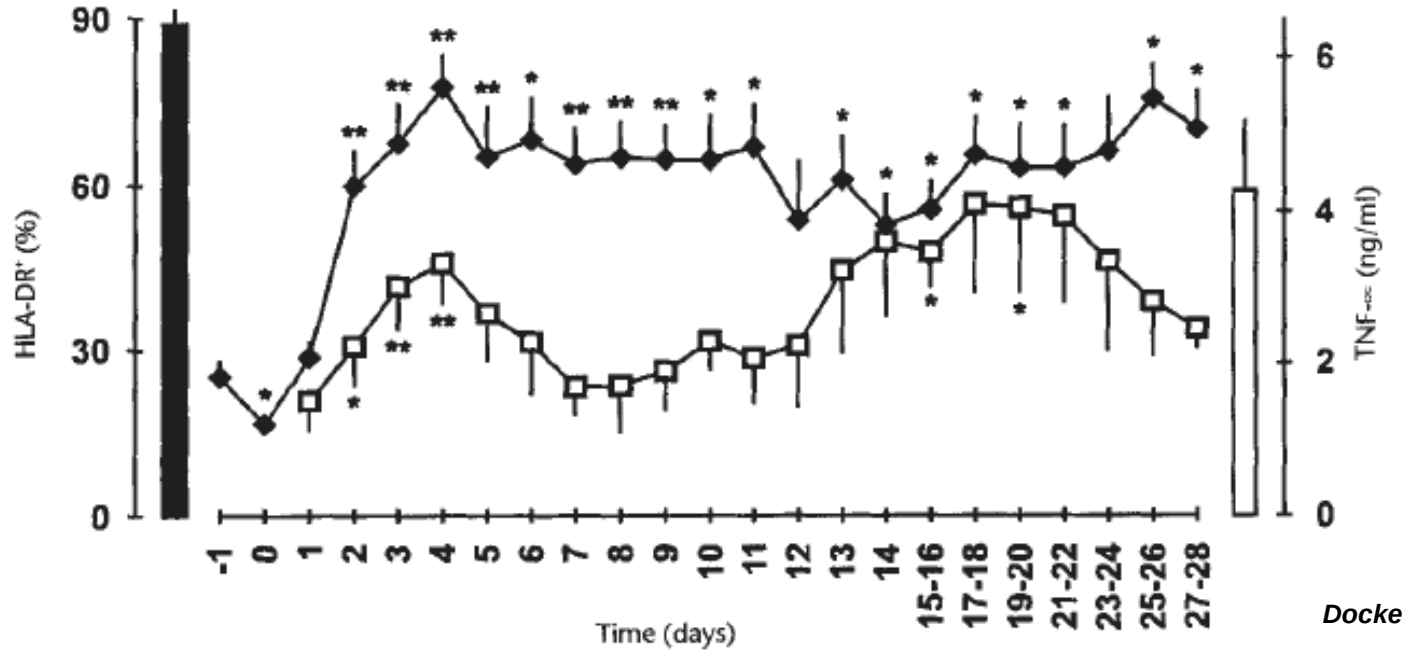




Meisel et al. AJRCCM 2009

Boost the Th-1 response

- **INF-γ is the prototypic Th-1 cytokines**
- **EMA/FDA approved for the orphan disease:**
  Progressive Septic granulomatosis (innate deficiency in NADPH oxydase)
- **Able to increase HLA-DR expression and TNF-α secretion by monocytes**



Docke et al. Nat Medicine 1997

- **Negative studies in post-surgical setting in the 90's** *(Mock et al. Shock 1996)*

Restore lymphocyte homeostasia

IL-7

- **cytokine with proliferative effect on T-cells, promote Th-1**
- **rh-IL-7 studied in HIV patients with persistent low CD4+ cells**
  (Thiébaut Clin infect Dis 2016)
- **Improves animal survival in diverse murine model of sepsis**
  (Unsinger J Immunol 2010 & J Immunol 2012, Shindo J Leuk Biol 2017)
- **Restores *ex vivo* septic lymphocytes function**

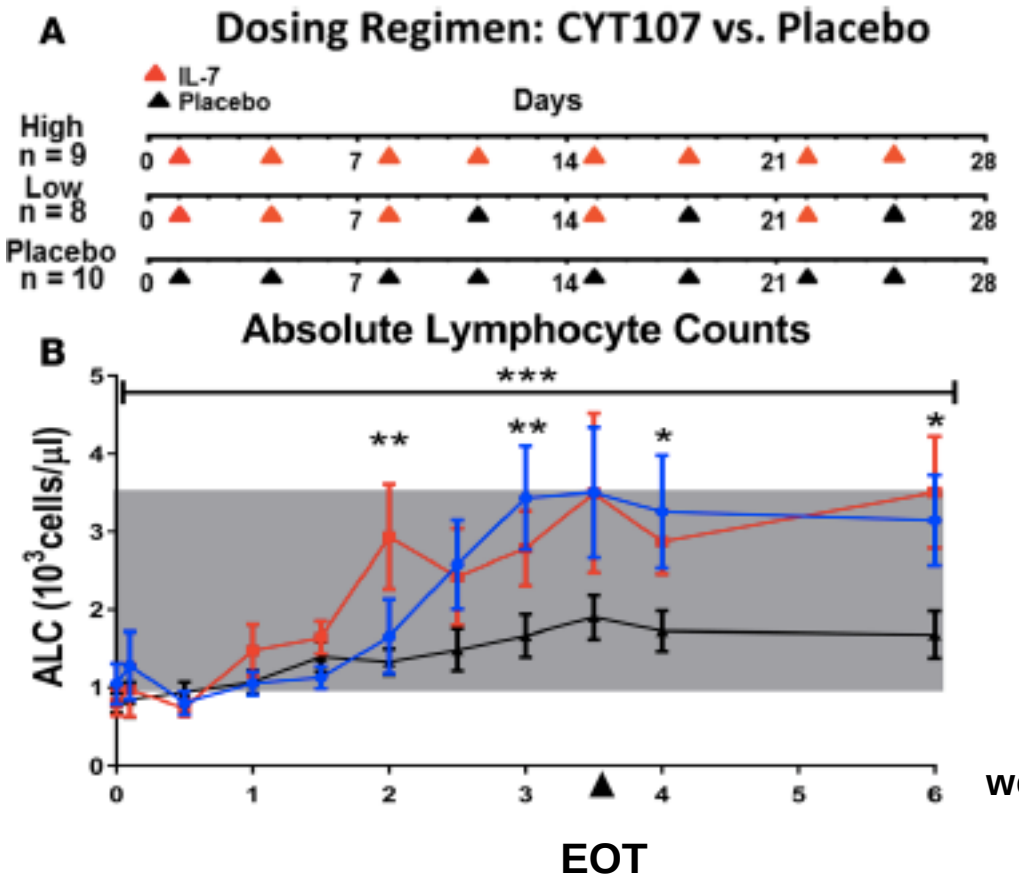
  (Venet J Immunol 2012)
- **phase 2 trial (US & France)**

JCI insight
CLINICAL MEDICINE

Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial

Bruno Francois,[1,2,3] Robin Jeannet,[2] Thomas Daix,[1,2] Andrew H. Walton,[4] Matthew S. Shotwell,[5] Jacqueline Unsinger,[4] Guillaume Monneret,[6,7] Thomas Rimmelé,[7,8] Teresa Blood,[4] Michel Morre,[9] Anne Gregoire,[9] Gail A. Mayo,[10] Jane Blood,[4] Scott K. Durum,[11] Edward R. Sherwood,[10,12] and Richard S. Hotchkiss[4,13,14]

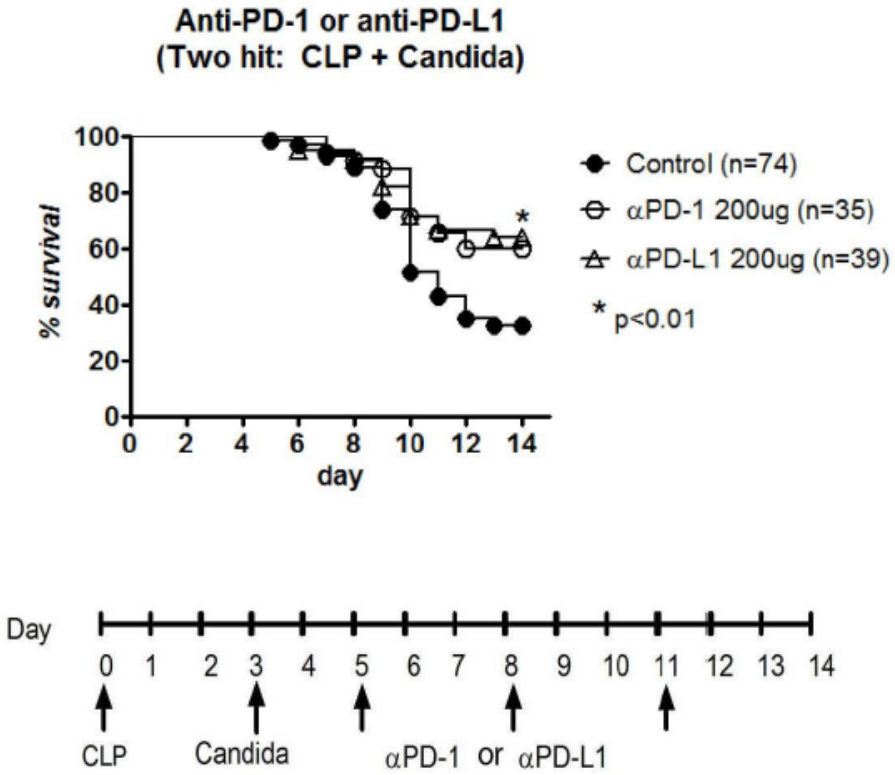
- Phase 3 in HIV
- 1st phase 2 in ICU
- N = 27 patients
- Septic shock
- ALC < 900/mm^3

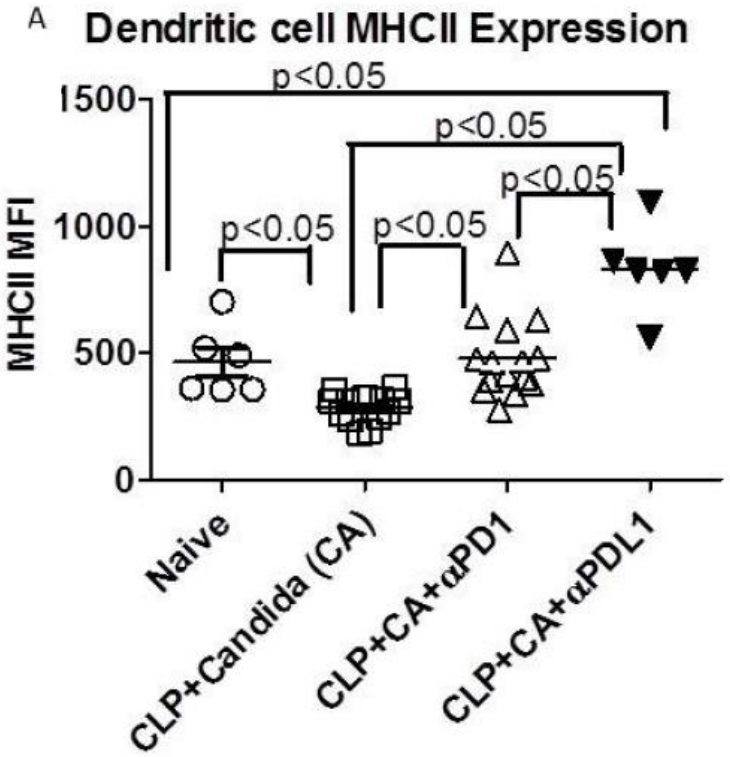


Francois et al. JCI insight March 2018

Targeting immune « check point »

Antibodies anti PD-1 or anti PD-L1





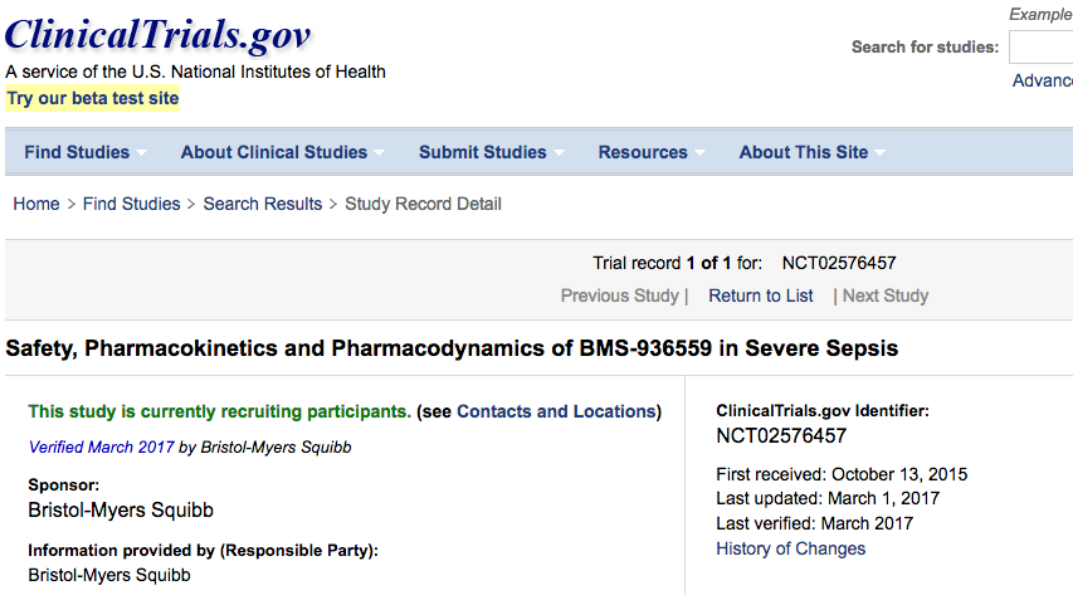
Chang et al. Crit Care 2013

Ex-vivo data demonstrating capability to restore normal function of T-cells

Chang et al. Crit Care 2014

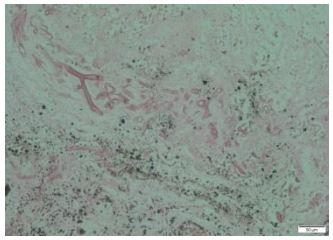
Targeting immune « check point »

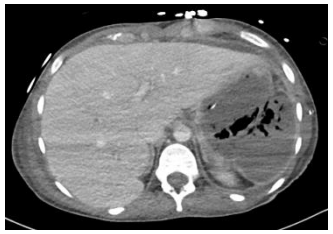
- **Extraordinary successful in oncology field**
- **2 phase 2 started in sepsis field (anti-PD-1 & anti-PD-L1)**



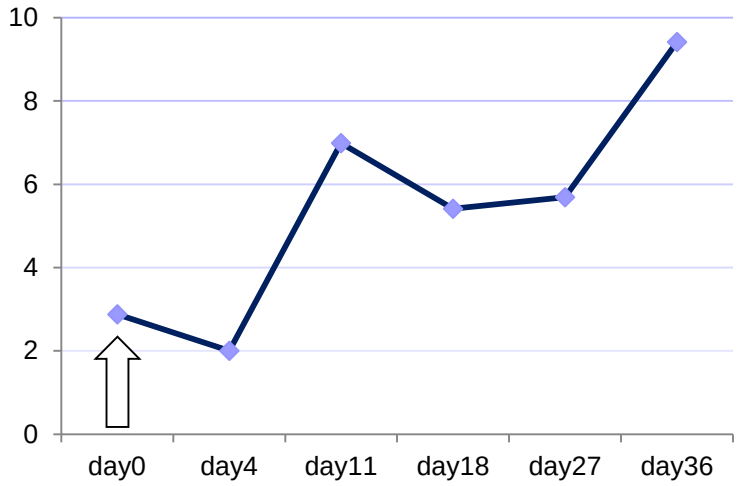
Targeted immunotherapy

Treatment of mucormycosis & immunopathy with Nivolumab (anti-PD1) + Interferon-γ

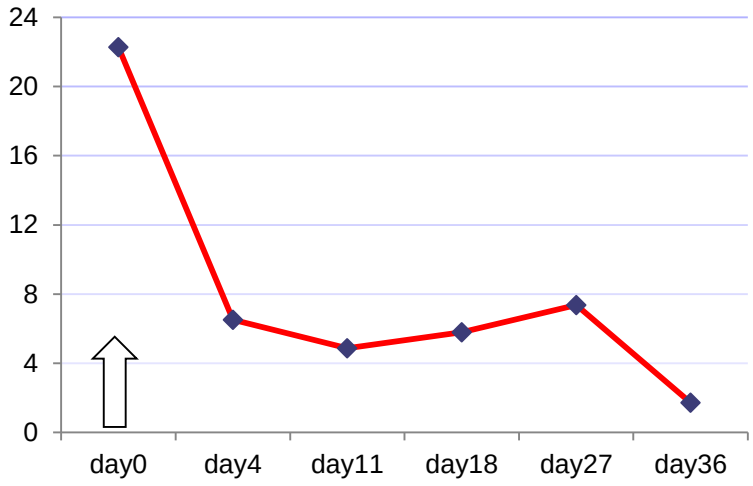




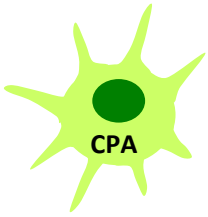
HLA-DR MFI



% CD4 PD-1 +



Reversal of monocytes deactivation



Inhibition of PD-1 expression

Grimaldi et al. Lancet Infect Dis 2017

Evolution

- Slow improvement, regression of shock, extubation after 15d
- 3 Abdominal CT in 2 month no signs of evolution
- Suffer from osteitis due to multi-drug resistant Klebsiella
- Leaved the ICU after 80 days
- Discharged from the hospital after 11 month
- Still needs reconstructive orthopedic surgery

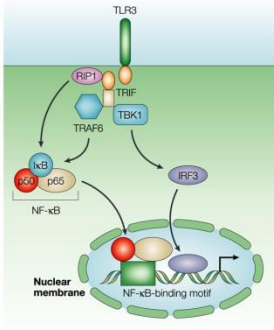
Grimaldi et al. Lancet Infectious Dis 2017

Conclusion

- **Immunopathie : complémentaire du paradigme classique du sepsis**
- **Association complexe de modifications immunologiques**
- **Impact clinique sur le risque d'infection nosocomiale**
- **Compréhension des mécanismes par des modèles animaux**
- **Stratégies thérapeutiques en cours d'essai**
- **Les patients cancéreux septiques seraient la cible idéale !**

Hôpital Erasme

ULB



Limites des études cliniques

- Etudes autopsiques
- Etudes monocentriques
- Mécanisme de déplétion inconnu : migration ? apoptose ? Ins. centrale ?
- Perturbations tissulaires non/mal étudiées
- Fonctionnalité des cellules difficilement étudiable
- Association statistique : pas de lien de causalité démontré
- End point = infections secondaires → pb définition / autres FDR
- Hétérogénéité des patients :
  - Source de l'infection
  - Pathogène
  - Délai depuis le début de l'infection
  - Age, comorbidités…
- Intérêt des modèles animaux dans une approche complémentaire

Dangers pour l'immunostimulation

- **Très larges études randomisées**
- **Sélection imprécise des patients**
- **Hétérogénéité trop forte**
- **Ratio signal-to-noise bas**

➔ **Résultats négatifs**

Prévenus par caractérisation des patients (immunophenotype) et suivi (immunomonitoring)

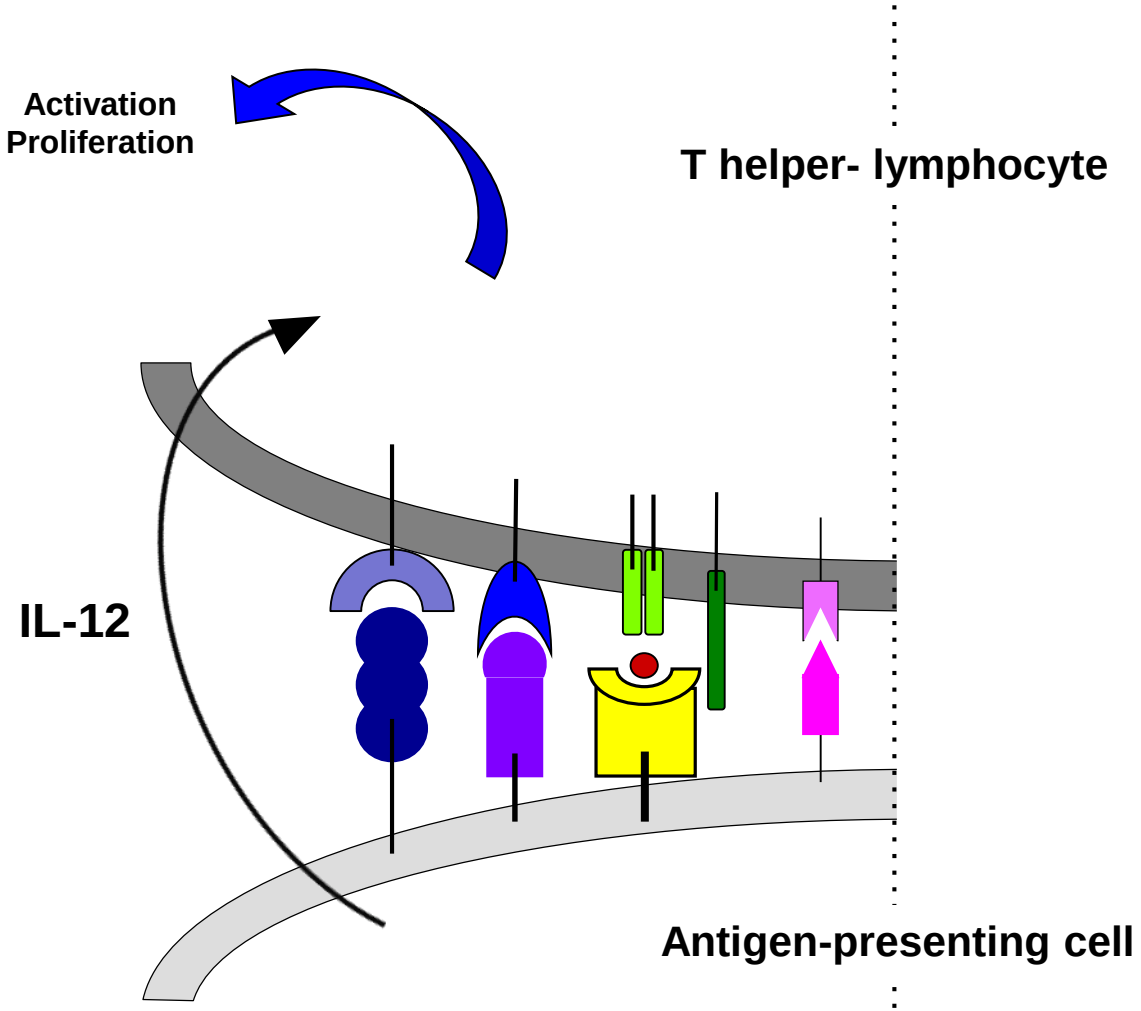
D. Grimaldi
S. Louis
F. Pène
G. Sirgo
C. Rousseau
Y. E. Claessens
L. Vimeux
A. Cariou
J. P. Mira
A. Hosmalin
J. D. Chiche

Profound and persistent decrease of circulating dendritic cells is associated with ICU-acquired infection in patients with septic shock

	Septic shock	Non-septic shock	Sepsis	*P*
Number of patients	43	29	16	
Female (%)	17 (39.5)	12 (41.4)	5 (31.25)	NS
Age (years)	67 (56.5–79)	68 (54–79)	67.5 (41–85)	NS
APACHE II	32 (27–35)	33 (28–41)	8 (4.75–10)	<0.0001
SAPS II	71 (61.5–83)	76 (60–87)	22.5 (13–27)	<0.0001
SOFA admission	10 (6.5–14)	10 (8–13)	0.5 (0–1)	<0.0001
Primary injury	Pneumonia 25 (58) Abdominal sepsis 7 (16) Other 11 (26)	Cardiogenic shock 12 (41) Cardiac arrest 12 (41) Hemorrhage 5 (17)	Pneumonia 8 (50) Urinary 4 (25) Other 4 (25)	NA
Leukocytes (G/L)	10.2 (7.2–20.5)	13.2 (8.6–17.6)	9.15 (5.4–11.8)	0.11
Lymphocytes (G/L)	0.42 (0.27–0.85)	1.01 (0.63–1.68)	1.27 (0.84–1.56)	0.0004
Length of ICU stay	9 (5–13)	4 (3–9)	NA	0.01*
Shock duration	3 (2–5)	3 (2–4)	NA	NS*
Death in ICU	16 (37.3)	11 (37.9)	NA	NS*
D1 SOFA	12 (9–14.5)	11 (8.5–14)	NA	NS*
D3 SOFA	8 (4–11)	8.5 (8–11)	NA	NS*
D7 SOFA	8 (4–11)	6 (4.5–8.5)	NA	NS*
Number of patients at D3	40 (93%)	17 (58.6%)	NA	
Number of patients at D7	23 (53.5%)	8 (27.6%)	NA	

Intensive Care Med 2011

Conventional adaptive immune response



Molecules at the APC side

- HLA-DR
- PDL-1 / PDL-2
- CD80 / CD86
- CD40

Molecules at the lymphocyte side

- CD3-CD4
- PD-1
- CD28
- CTLA-4
- CD40 -L