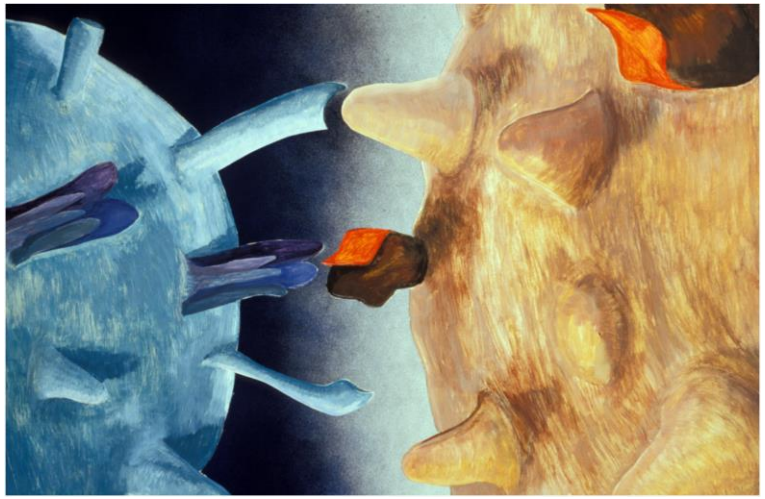
Immunothérapie et sepsis :

Le sepsis une (des) maladie(s) dysimmunitaire(s) ?



Benjamin Gaborit EA3626- JNI 2018

département des Maladies Infectieuses
UNIVERSITÉ DE NANTES

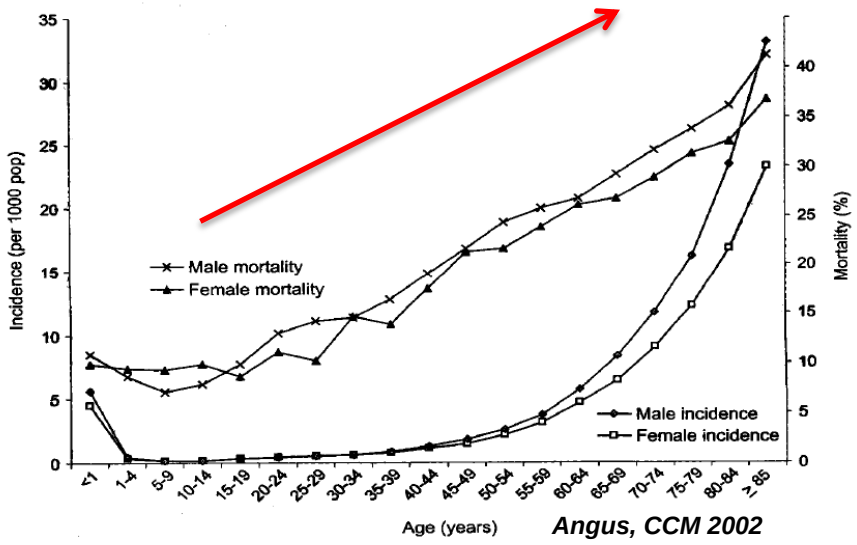
Déclaration d'intérêts de 2014 à 2017

- **Intérêts financiers : Aucun**
- **Liens durables ou permanents : Aucun**
- **Interventions ponctuelles : Aucun**
- **Intérêts indirects : Aucun**

1- Le sepsis : Quels sont les enjeux en 2018 ?

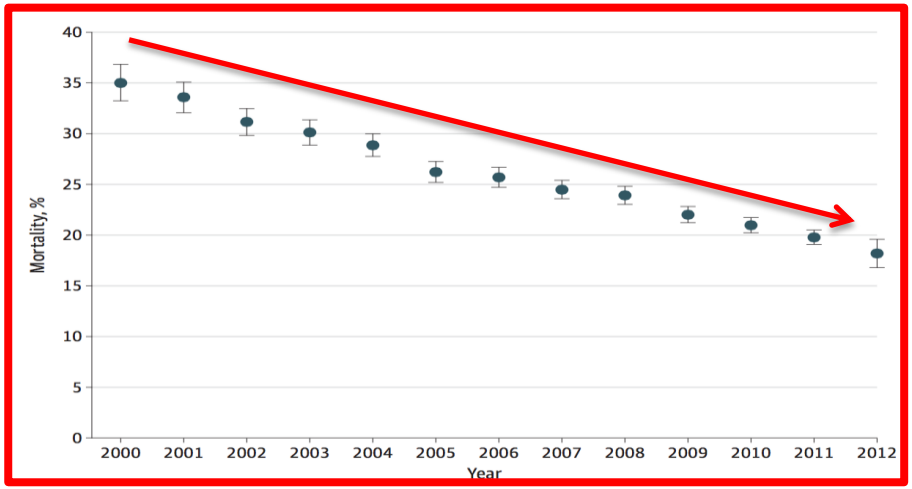
- **3ième cause de décès dans les pays industrialisés**
- **⬆ incidence globale** (256 à 335 /100 000 en Allemagne 2007-2013)

Evolution de la mortalité du sepsis et choc septique



Angus, CCM 2002

- ⇧ **Thérapeutiques immunosuppressives**
- **Vieillissement de la population**
- **⇧des patients ID**



Kaukonen KM et al. JAMA. (2014) (n:101 064, 171 centres)

- **Amélioration de la prise en charge initiale**
- **Mais différentiel net : ⬆ mortalité globale**

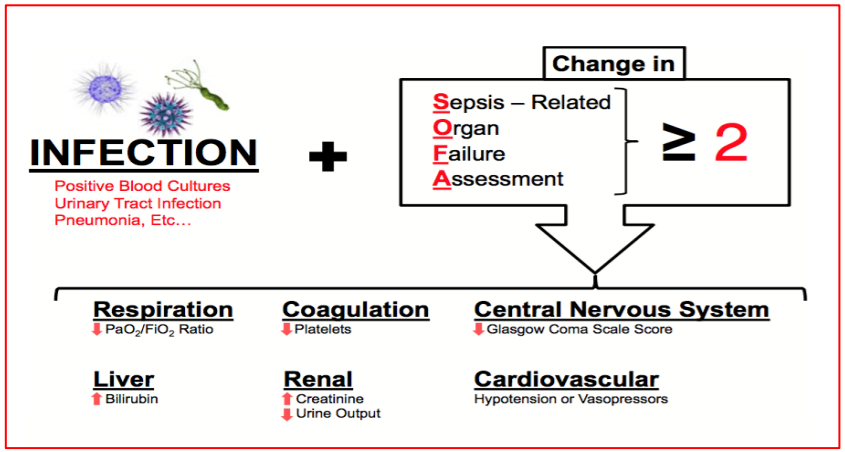
Fleischmann, C. et al. Dtsch. Arztebl. Int. 113, 159–166 (2016).

* Hotchkiss RS, Rev Dis Primers. 2016 Jun 30;2:16045
Sundararajan, *Crit. Care Med.* 33, 71–80 (2005).
Fishman JA. Infect Dis Clin North Am 2010

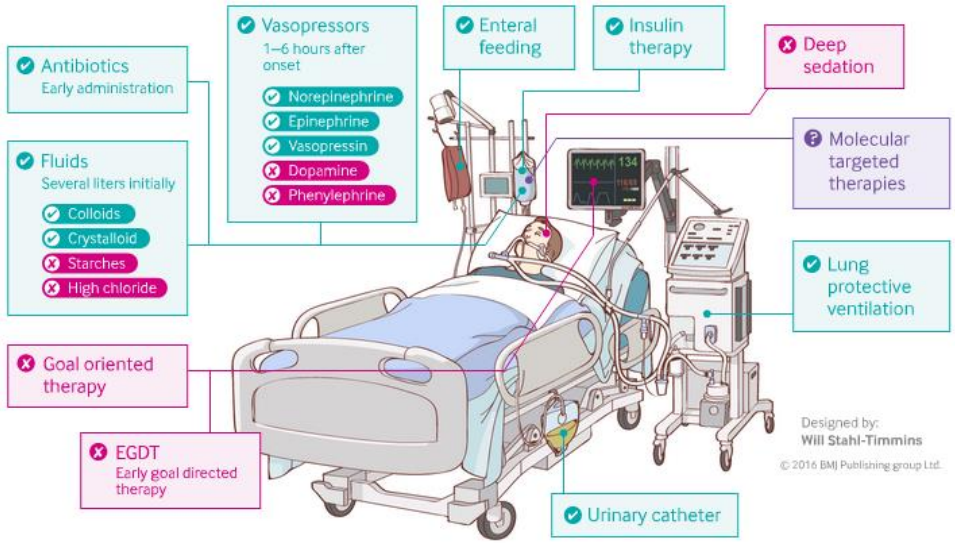
2- L'optimisation des prises en charge a fait reculer la mortalité précoce !

- **En 2016 définition basée sur la mortalité précoce (SOFA≥2) : 10% mortalité**
- **Choc septique : 30 -40%**

= reconnaître précocement
les patients qui décèdent vite



Le traitement d'une dysrégulation immunitaire :
« Une réaction inflammatoire excessive en réponse à un agent infectieux »



- **Mortalité Précoce : hospitalière, J28**

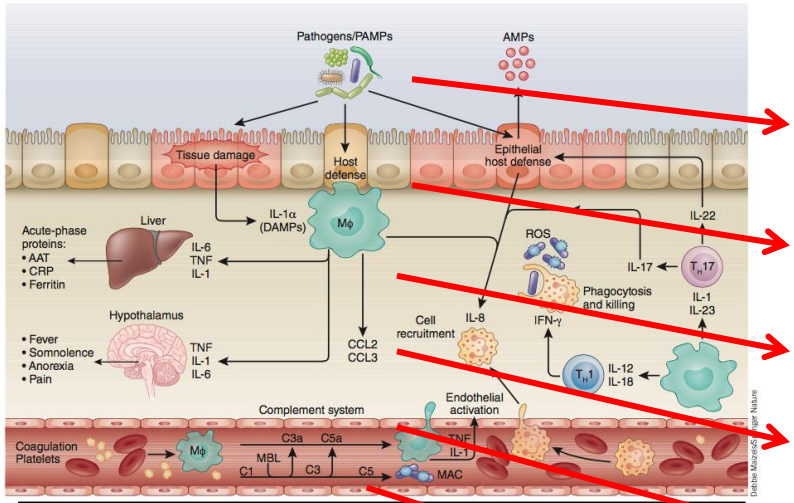
- **Comment faire mieux ?**

Singer JAMA 2016

Gotts JE.BMJ. 2016.

20 ans d'essais thérapeutiques « anti-inflammatoire »

= + de 150 études ..



= identification précoce des + graves les plus inflammatoires

La bonne stratégie ?

= Changement de paradigme

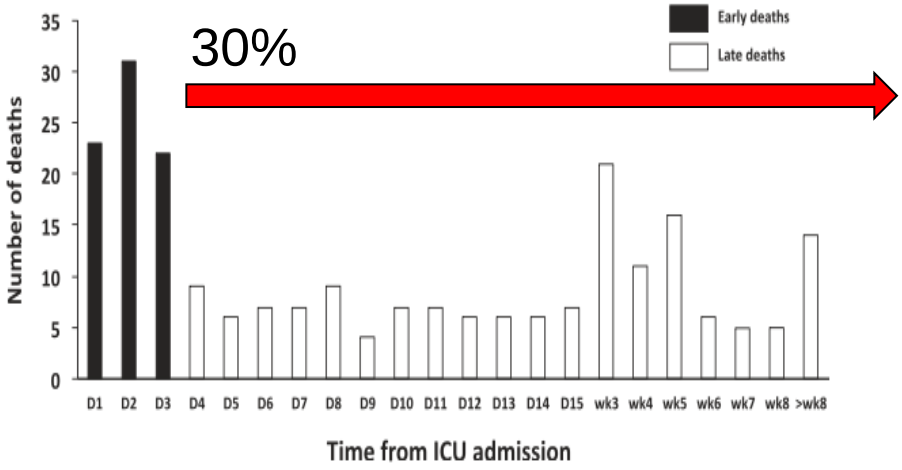
Table 2 | **Selected clinical biological response modifiers used in clinical trials for severe sepsis or septic shock**

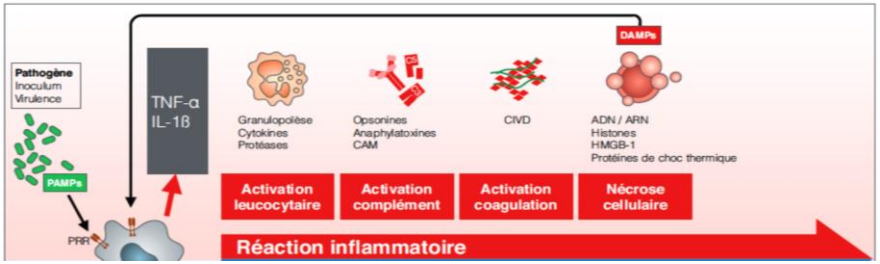
Target	Class	Study type	Drug	Finding	Refs
Endocrine abnormalities	Corticosteroids	Meta-analysis	Corticosteroid	No or modest effect	173,174
	Vasopressors	Prospective RCT	Arginine vasopressin	No effect	175
Endotoxin	Monoclonal antibody	Prospective RCT	HA-1A	No effect	176,177
			E5	No effect	
	Lipid emulsion	Prospective RCT	GR270773	No effect	178
	Bactericidal-permeability increasing peptid	Prospective RCT	rBPI21	Modest effect	179
TLR4	Monoclonal antibody	Prospective RCT	TAK-242	No effect	180,181
			Eritoran tetrasodium	No effect	
CD14	Monoclonal antibody	Prospective RCT	IC14	Unclear	182
TNF	Monoclonal antibody	Prospective RCT	BAY 1351	No effect	183,184
				No effect	
	Immunoadhesin	Prospective RCT	Lenercept	No effect	124,185
			Etanercept	No effect	
IL-1	Receptor antagonist	Prospective RCT	Anakinra	No effect	186
PAF	PAF antagonist	Prospective RCT	TCV-309	No effect	187,188
			Lexipafant	No effect	
Eicosanoids	NSAIDs	Prospective RCT	Ibuprofen	No effect	189
	Soluble phospholipase A2 inhibitor	Prospective RCT	Varespladib	No effect	190
C5a	Monoclonal antibody	Prospective RCT	CaCP29	Ongoing	49
Nitric oxide	L-N-methylarginine	Prospective RCT	546C88	Modest effect	191
	Reducing agents	Prospective RCT	Methylene blue	Modest effect	192
Hypercoagulability or disseminated intravascular coagulation	Activated protein C concentrate	Prospective RCT	Drotrecogin alfa (activated)	Beneficial	141,193
				No effect	
	Tissue factor pathway inhibitor	Prospective RCT	Tifacogin	No effect	194
	Antithrombin	Prospective RCT	Antithrombin	No effect	195
	Anti-tissue factor antibody	Prospective RCT	ALT-836	No effect	196
	Heparin	Meta-analysis	Heparin salt	Modest effect	197
	Thrombomodulin	Prospective RCT	ART-123	Modest effect	198

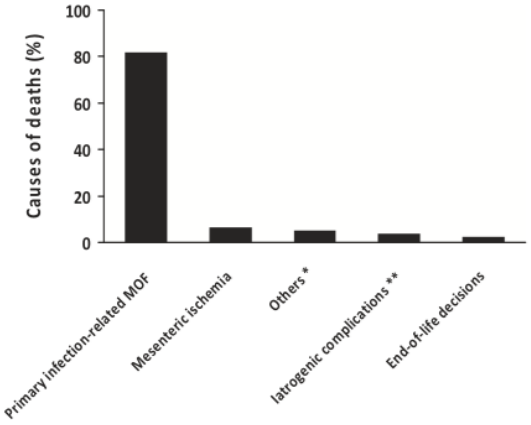
Netea MG Nat Immunol. 2017 Jul 19;18(8):826-831

Hotchkiss RS, Nat Rev Dis Primers. 2016 Jun 30;2:16045.

La mortalité du sepsis en réanimation ?

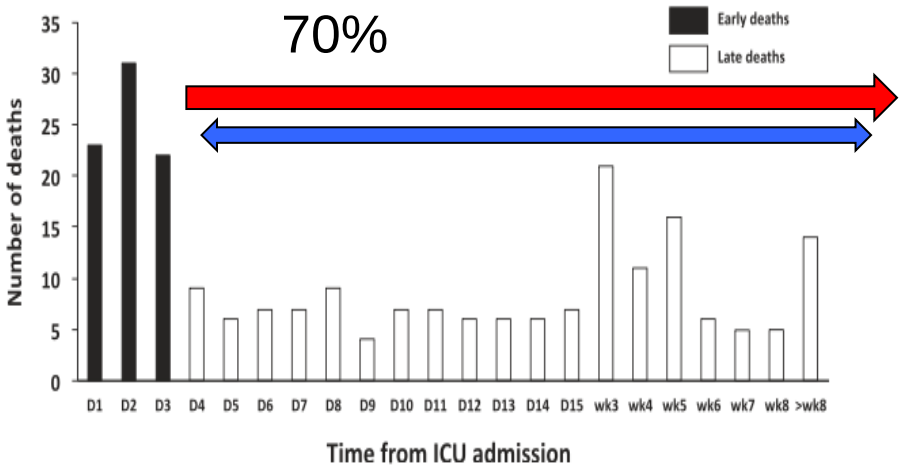


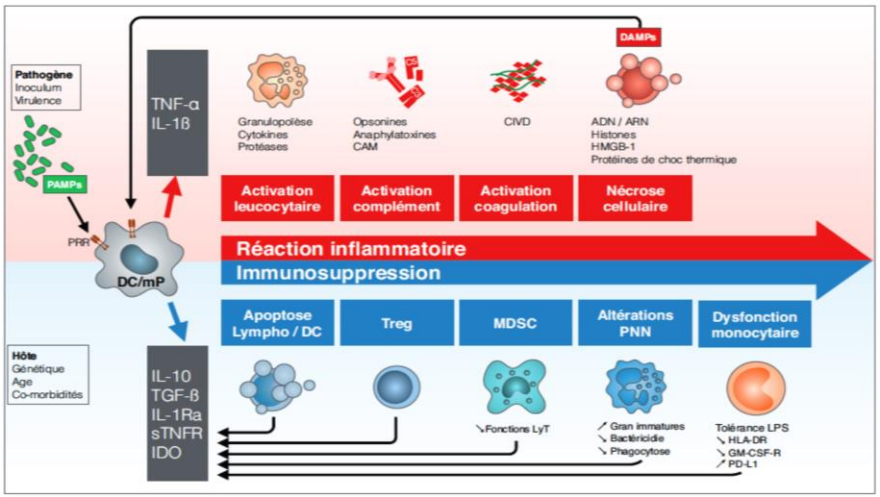




Daviaud – F.Pène. Annals of Intensive Care (2015) 5:16
(n: 543, 6 ans 2008-2013)

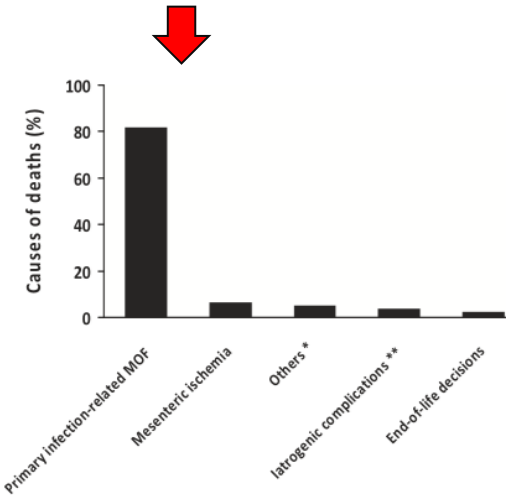
Les patients survivants, sont-ils guéris ?

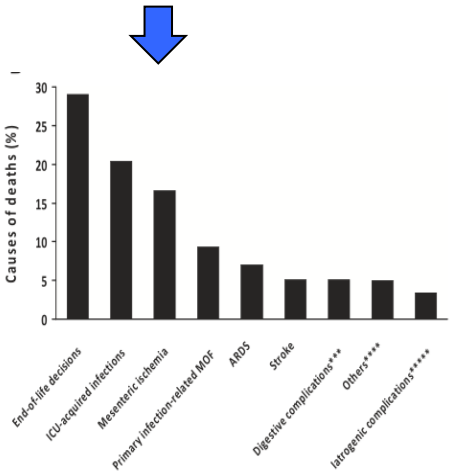




Dès J3, 40% des patients présentent des manifestations cliniques d'immunoparalysie :

- **les + sévères initialement**
- **↑ Infections nosocomiales (30%)**
- **↑ réactivations virales**



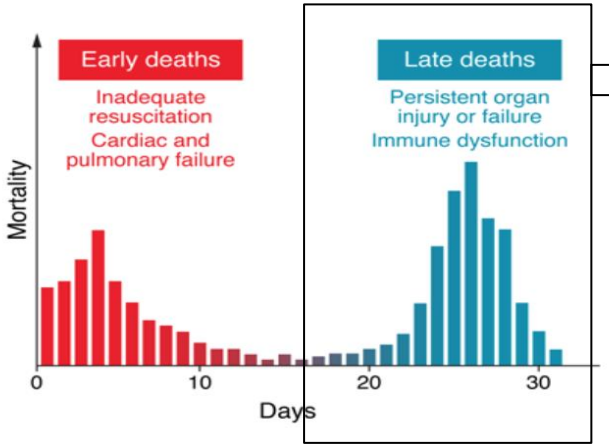


J. Stortz shock 2018

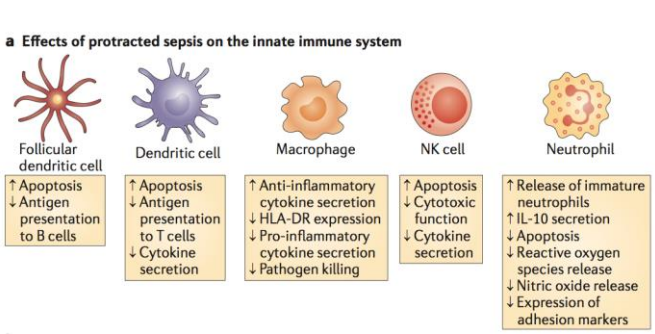
Prescott,BMJ 2016

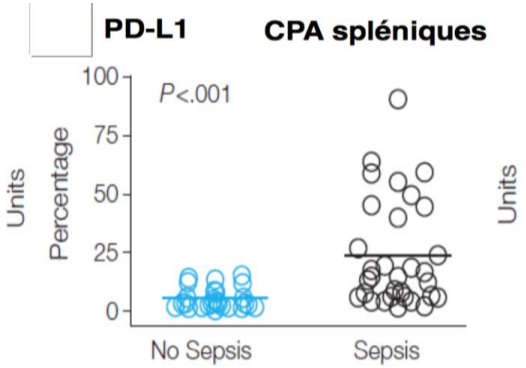
Landelle Infect Control Hosp Epidemiol 2008

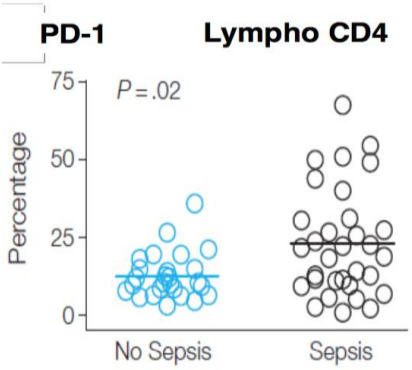
Le concept de « l'IS post septique » : immunologique ?



Atteinte de l'immunité innée et adaptive :



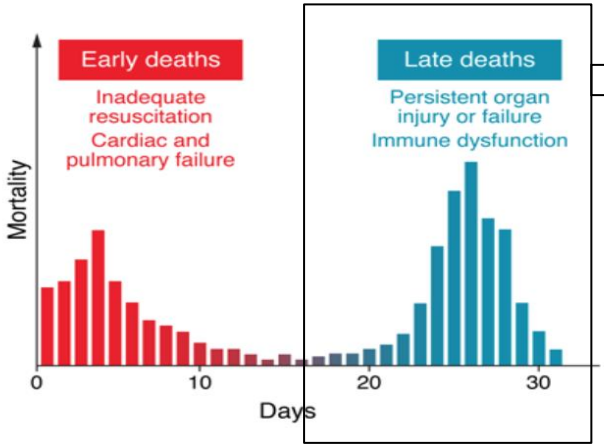




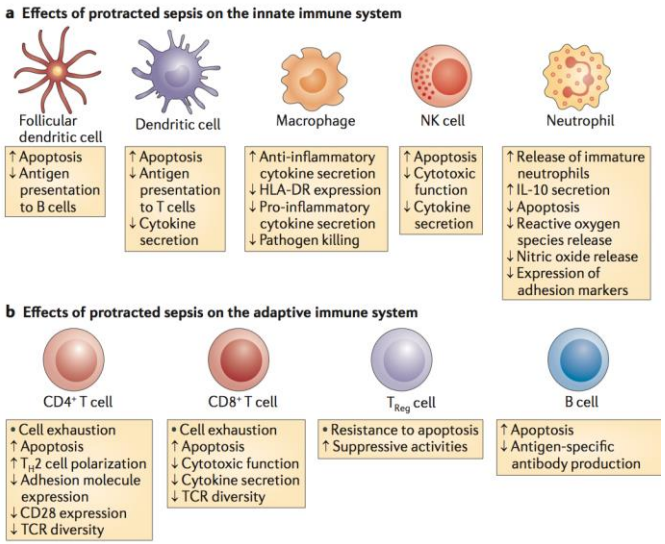
Hotchkiss RS et al., J immunol 2001

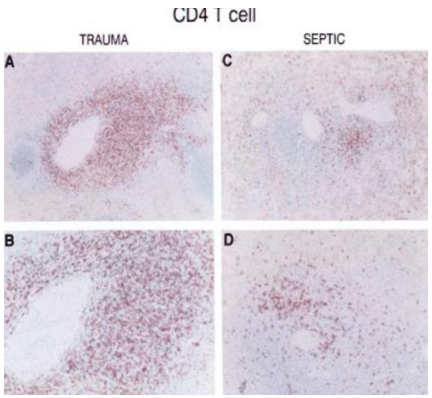
Boomer et al. JAMA 2011

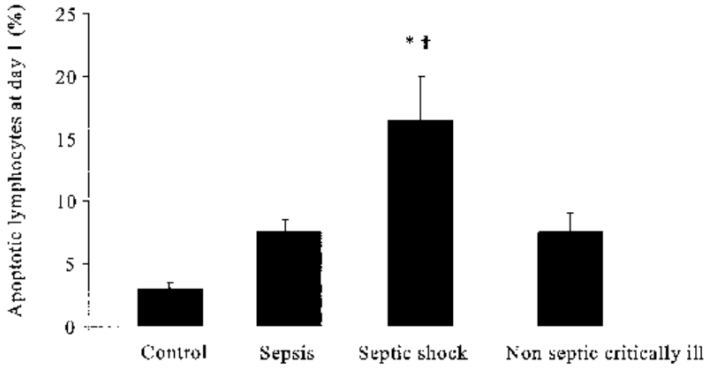
Le concept de « l'IS post septique » : immunologique ?

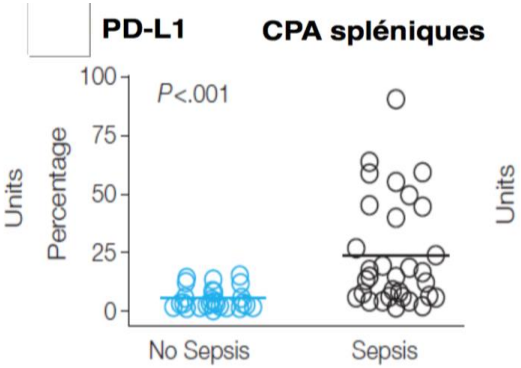


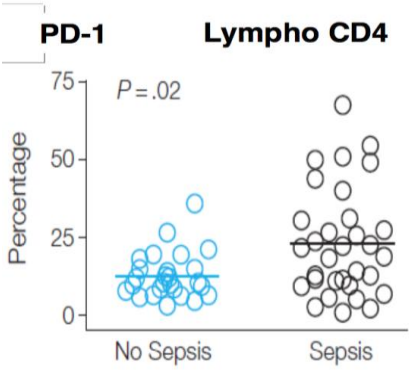
Atteinte de l'immunité innée et adaptive :







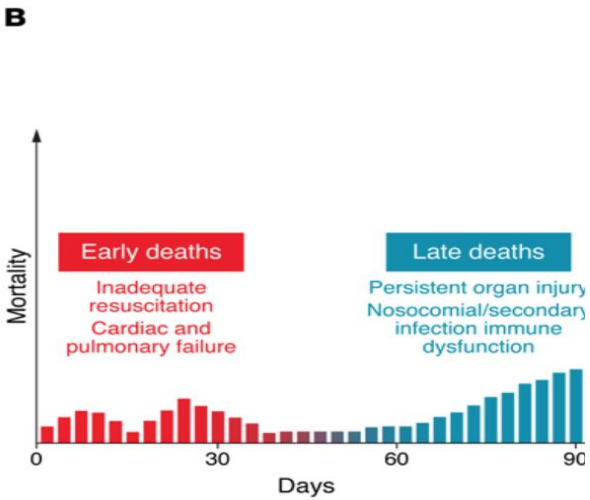




Le tulzo Shock 2002

Boomer et al. JAMA 2011

Et après la réanimation ?

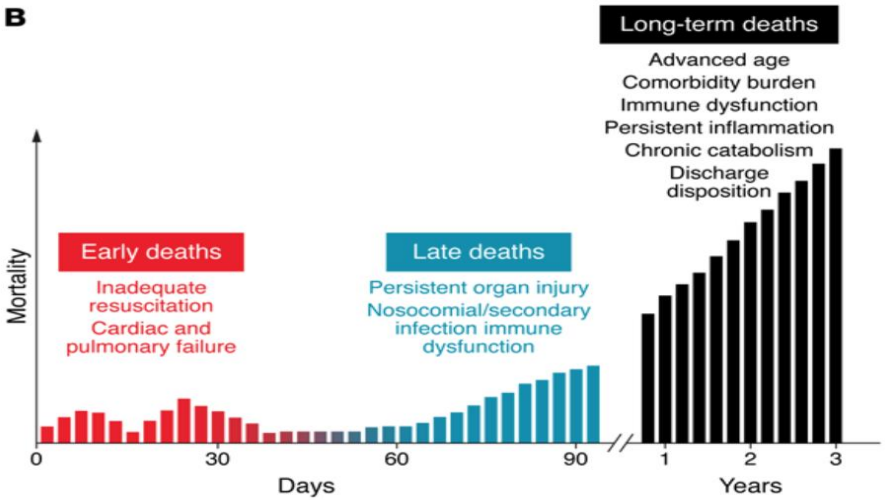


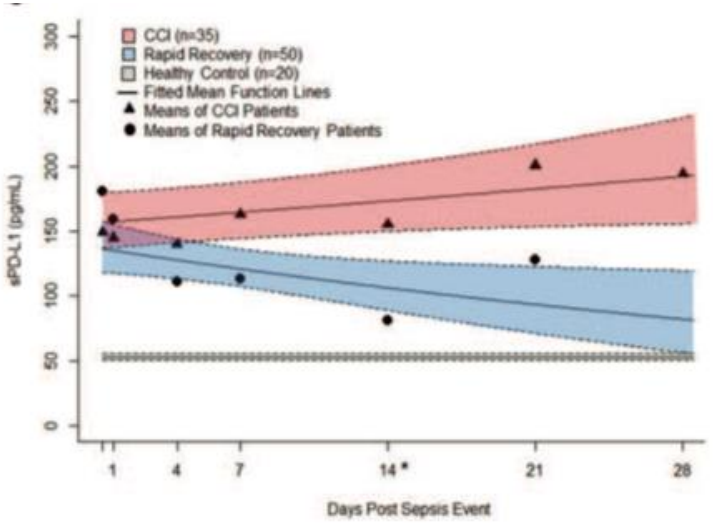
SHOCK, Vol. 49, No. 3, pp. 249–258, 2018

EVIDENCE FOR PERSISTENT IMMUNE SUPPRESSION IN PATIENTS WHO DEVELOP CHRONIC CRITICAL ILLNESS AFTER SEPSIS

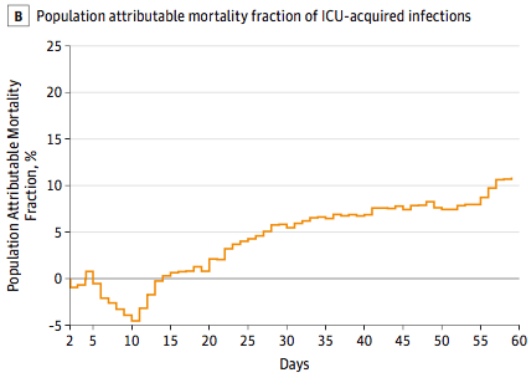
Adam Linder CCM 2014

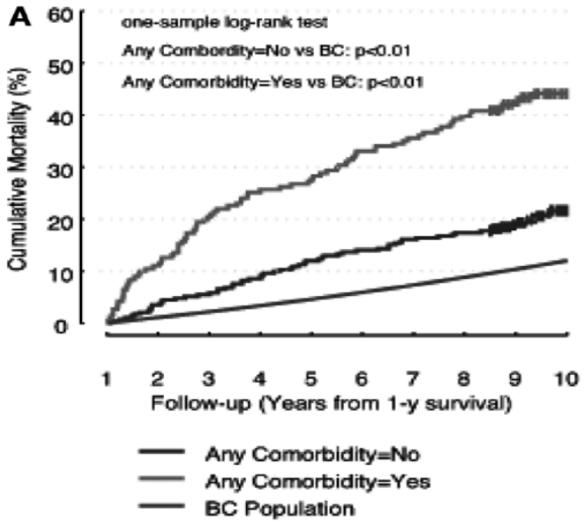
Et après la réanimation ?





- **20% de décès dans l'année post réa**
- **Infections tardives : + 30%**
- **Mortalité imputable à 2 ans : + 20%**
- **Troubles cognitifs**
- **Qualité de vie**

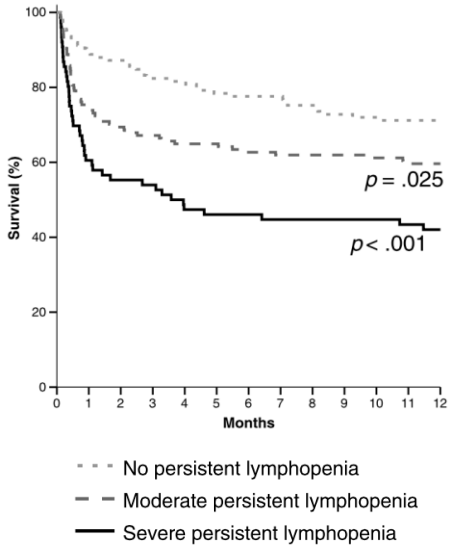


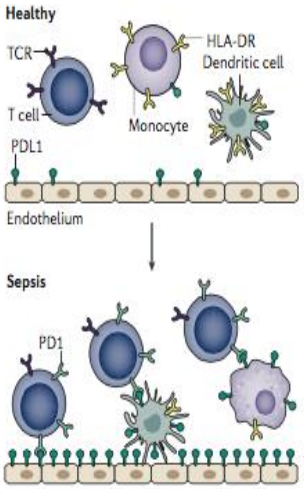


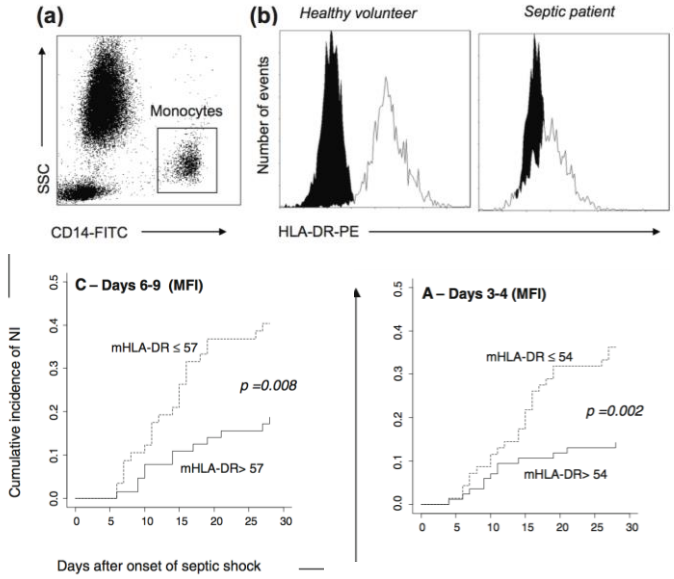
**Lonneke A. van Vught MARS concsocium JAMA 2016 (n:1 719)*
Stortz ET AL. SHOCK 2018 (n:88)
Adam Linder CCM 2014 (n: 2 200)
Gayat et al. Critical Care (2018) 22:8 (n:1 500, 21 réa)

Comment identifier ces patients en pratique ?

- **Les marqueurs biologiques les plus robustes et les plus validés :« Simple et efficace »**







Le Compte des Lymphocytes J4 :

- **Facteur pronostique (mortalité)**
- **Rôle directe dans l'IS**
- **Apoptose + « T cell exhaustion »**

↓ HLA DR monocytes :

- **CMH II « synapse immunologique »**
- **Méthode standardisée**
- **reproductible**
- **++ persistance <30% (5000 mAb/cell) à J3/4**
- **Corrélation infection II/mortalité.**

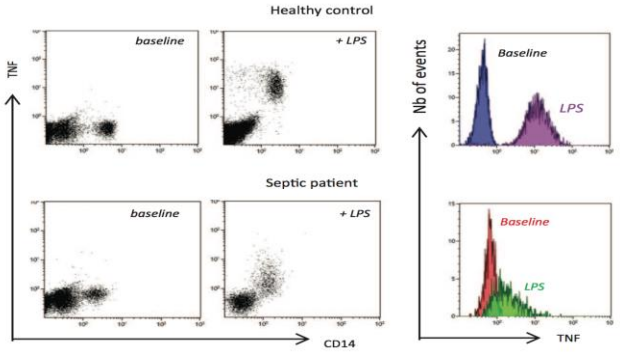
Critère d'inclusion utilisé dans les études en cours: GM-CSF (GRID), IL7

Drewry, Hotchkiss Shock 2014 (n:335)
Stortz . SHOCK 2018
Boomer JAMA. 2011;306(23):2594-2605
Landelle, Moneret ICM 2010 (n:209)

Quels marqueurs biologiques en développement ?

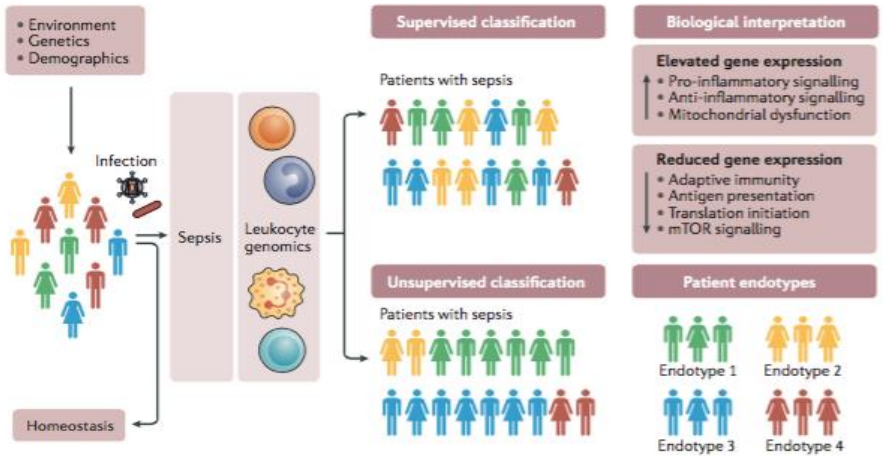
- **Simplification et standardisation des tests**

- **Test fonctionnel cytokine intracellulaire**
  - TNF monocytaire corrélé à HLA DR



** Monneret Shock 2017 (n:60)*

- **Etude transcriptomique :**
  - Transcriptome (RNA seq) du sang total
  - Définition de groupes homogènes de patients



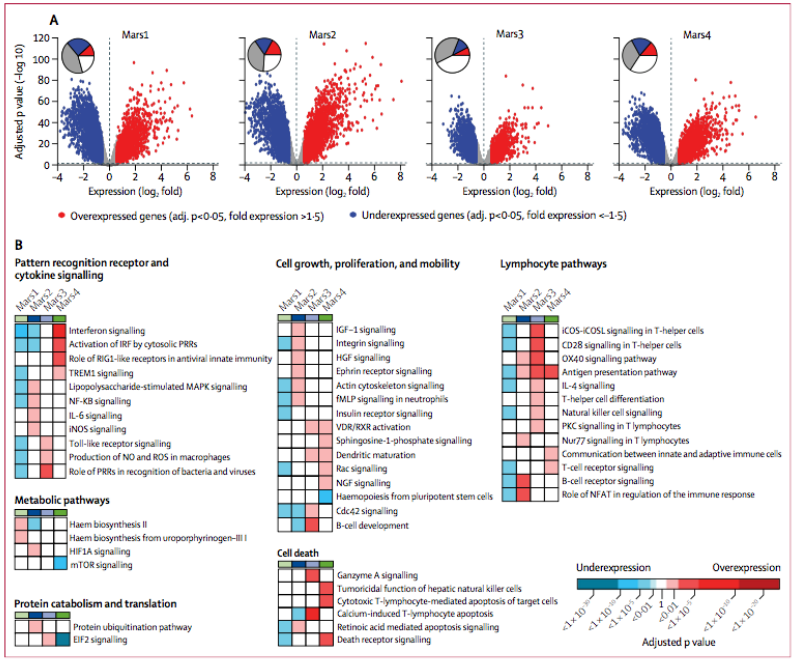


Figure 5: Biological interpretation of sepsis molecular endotypes

**Zouiouich et al. Intensive Care Medicine Experimental (2017) 5:39*
Stortz ET AL. SHOCK 2018
B. Scicluna Lancet Respir Med 2017; 5: 816–26
Tom van der Poll NATURE REVIEWS | IMMUNOLOGY 2017 (n:306)

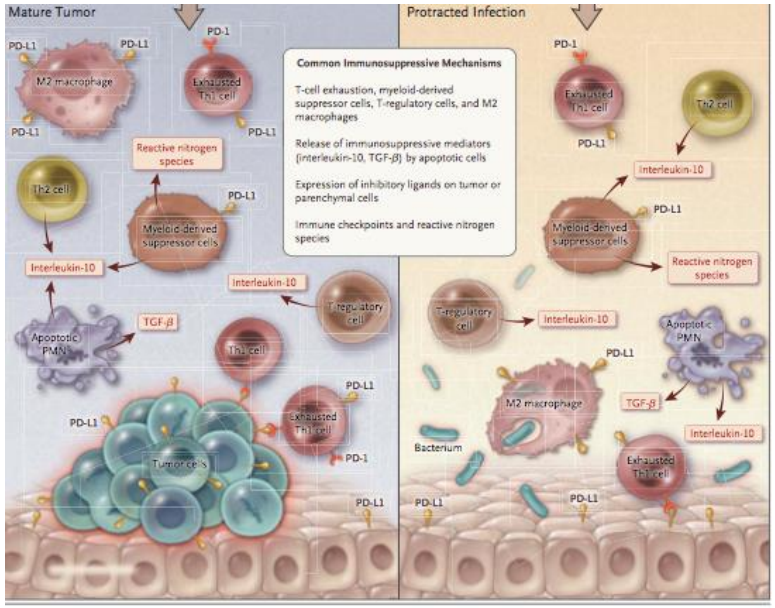
Quels traitements spécifiques de l'IS ?

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.



Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

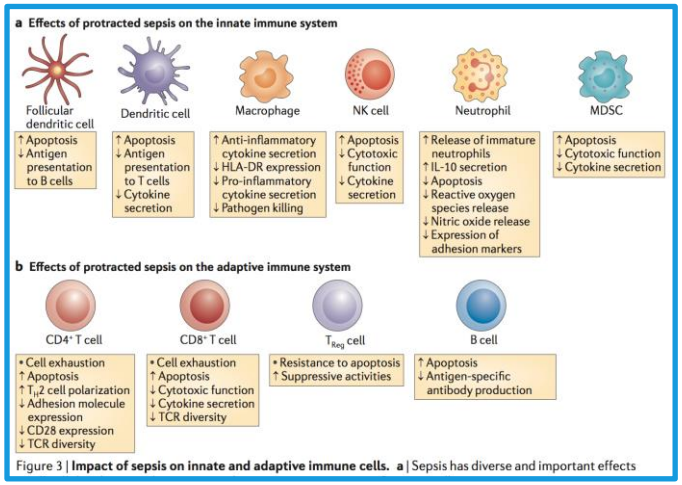
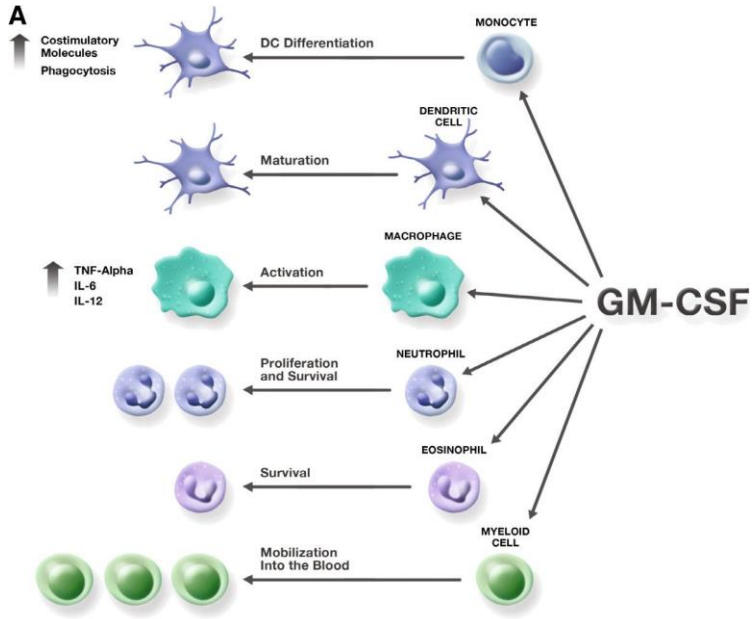


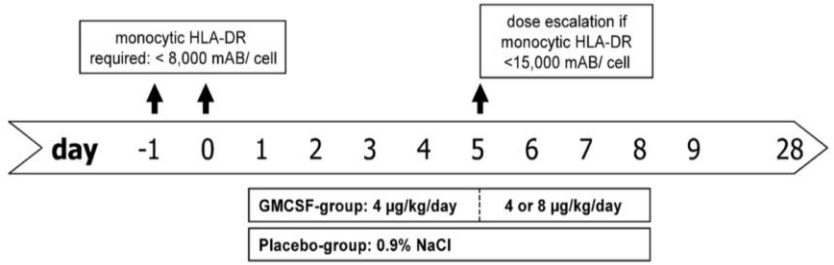
Figure 3 | **Impact of sepsis on innate and adaptive immune cells.** **a** | Sepsis has diverse and important effects

- **L' avancée des Essais cliniques et thérapeutiques :**
  - Le **GM-CSF**
  - Les **Cytokines immunostimulantes IL7-INFγ**
  - Le **blocage des signaux de co-stimulation négatifs PD1**

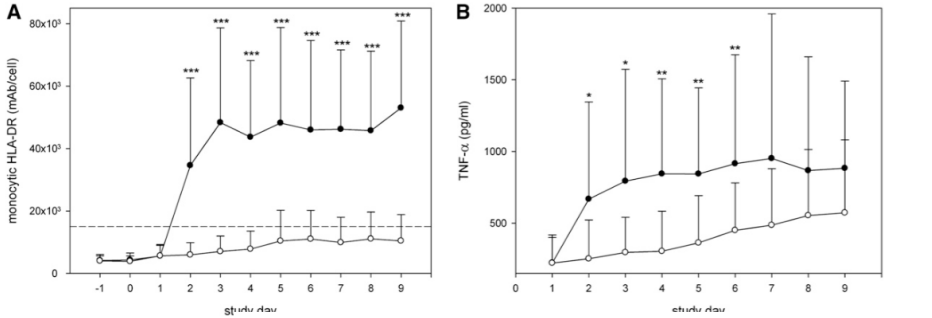
2- Les études en cours : Leucocyte granulocyte factor



Phase II : (n:39) GM-CSF 8 jours

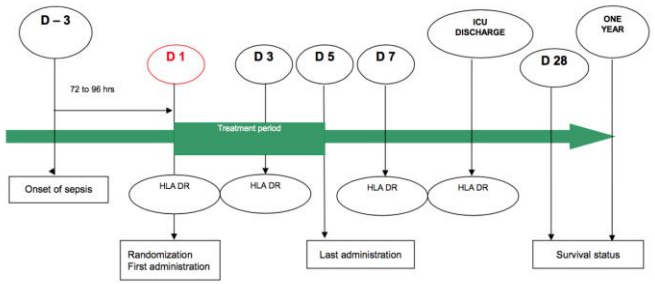


AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 180 2009



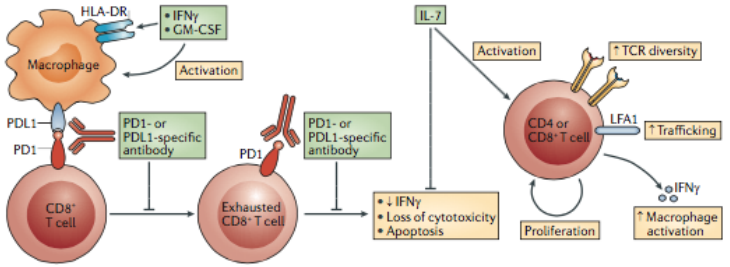
Etude GRID (Phase III) résultats en attente

- Inclusion de 100 patients
- Résultats attendus 2018



Meisel, Schefold, Pschowski, et al.: GM-CSF in Sepsis

2- Les études en cours : Cytokines immunostimulantes IL7



Mackall, C. L. Nat. Rev. Immunol.

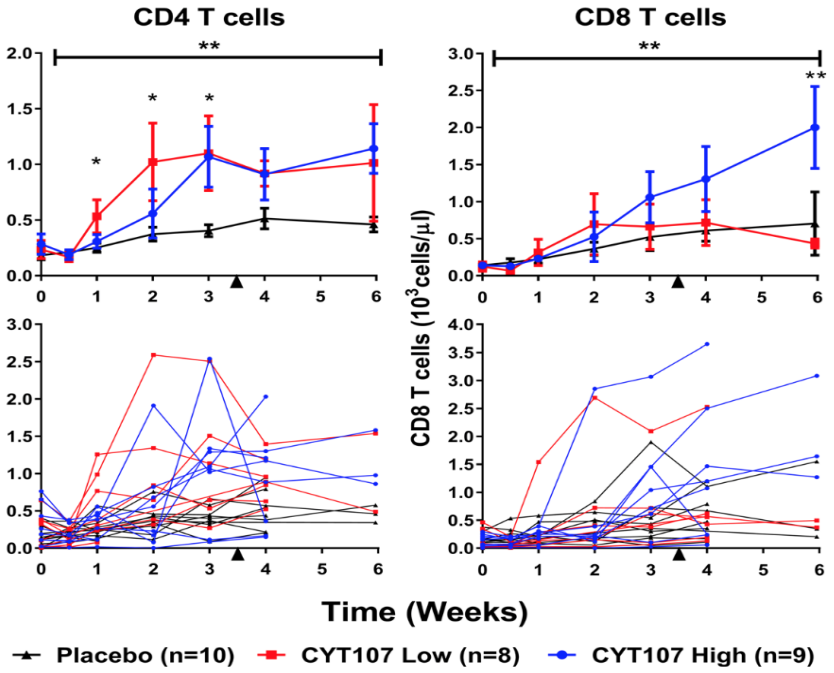
- Produit par le Thymus et MO
- Permet la différenciation Teff
- Case report (lymphopénieVIH/LEMP/idio)
- Étude préclinique
  - **Réduction de la lymphopénie**
  - Restauration de la **production IFNγ**

Etude IRIS-study (Phase II)

- Critère d'inclusion : lymphopénie < 900/mm3
- (n:39) 2 doses Safety

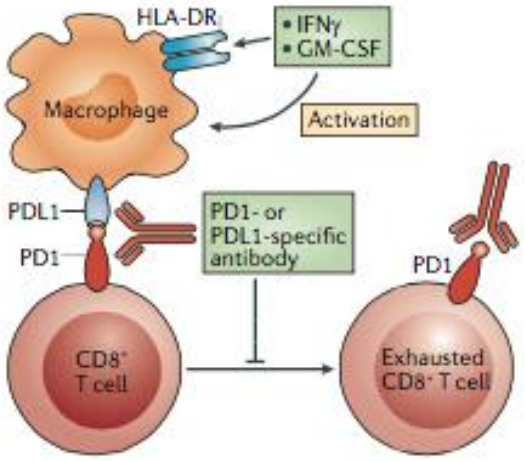
Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial

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]



Hotchkiss RSNat Rev Immunol. 2013 Dec;13(12):862-74

2- Les études en cours : Cytokines immunostimulantes INFγ



- **TH1 cells**
- activ**ator of monocytes**
- **Induit la phagocytose**
- 1997 étude ouverte - 2002 IFNγ inhalé chez le polytraumatisé

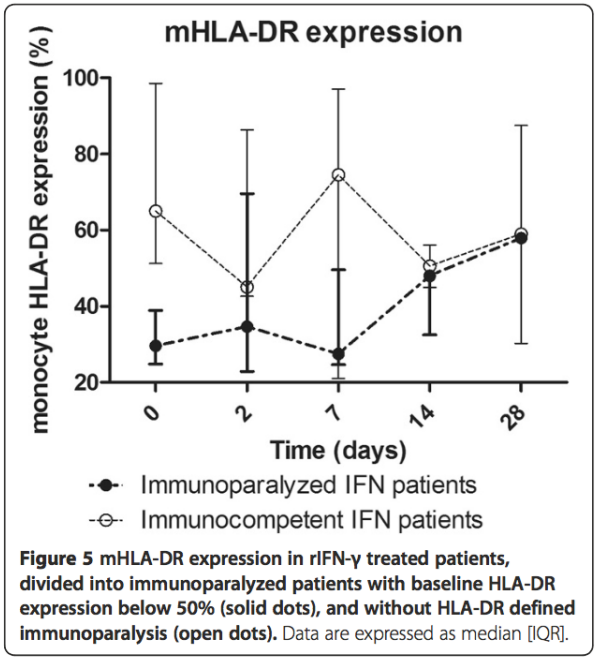


Figure 5 mHLA-DR expression in rIFN-γ treated patients, divided into immunoparalyzed patients with baseline HLA-DR expression below 50% (solid dots), and without HLA-DR defined immunoparalysis (open dots). Data are expressed as median [IQR].

Étude en cours (Phase III) :
- ClinicalTrials.gov : NCT01649921 (TNF/mono LPS) pays bas
- ClinicalTrials.gov : NCT03332225 (HLA RD) Grèce INF si IS inh IL1 si SAM

Delsing et al. BMC Infectious Diseases 2014, 14:166
http://www.biomedcentral.com/1471-2334/14/166

BMC Infectious Diseases

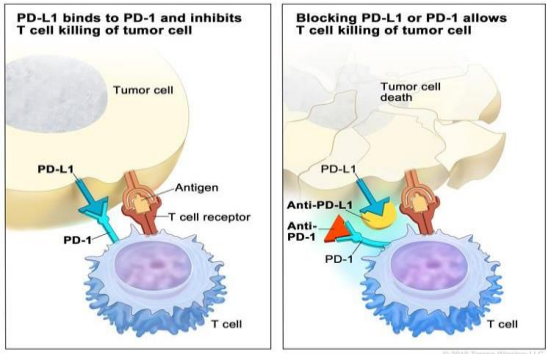
RESEARCH ARTICLE Open Access

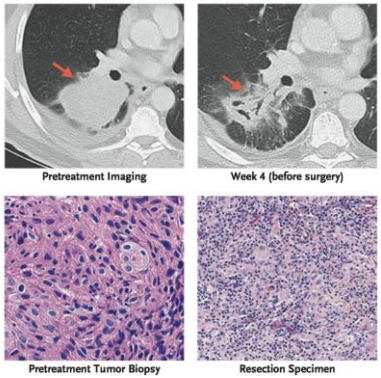
Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series

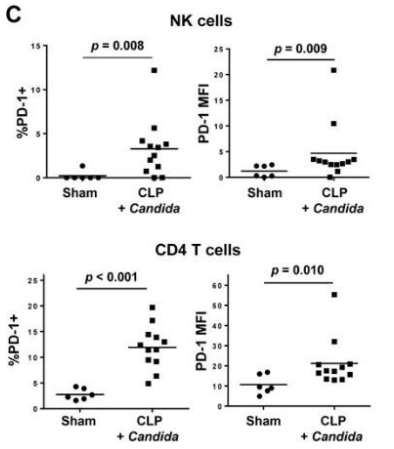
Corine E Delsing[1†], Mark S Gresnigt[1†], Jenneke Leentjens[1,2†], Frank Preijers[4], Florence Allantaz Frager[5], Matthijs Kox[2,3], Guillaume Monneret[5], Fabienne Venet[5], Chantal P Bleeker-Rovers[1], Frank L van de Veerdonk[1], Peter Pickkers[2], Alexandre Pachot[5], Bart Jan Kullberg[1] and Mihai G Netea[1,6*]

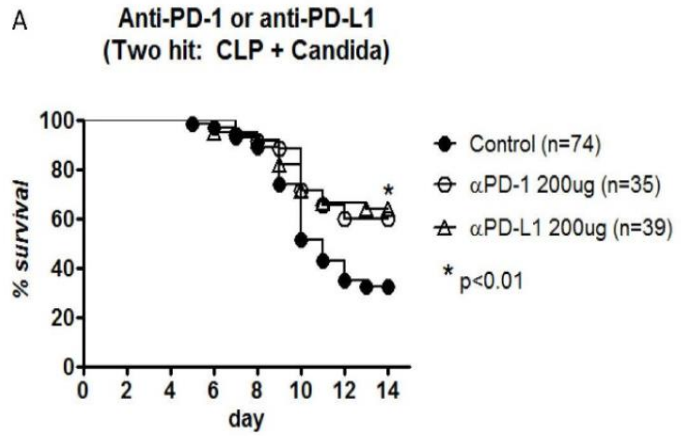
2- Les études en cours : blocage des signaux de co-stimulation négatifs PD1

PD1









- Anti PD1 en 2018 (BMS)
- Anti PD1L (BMS936559), Phase II Hotchkiss , lymphopénie < 1100 (n:24), SAFETY +, HLA DR

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

Anti-Programed Cell Death Ligand 1 Peptide Improves Survival in Sepsis

Yuichiro Shindo, MD[1,2,3], Jacquelyn S. McDonough, B.S.[1], Katherine C. Chang, PhD[1], Murali Ramachandra, PhD[4], Pottayil G. Sasikumar, PhD[4], and Richard S. Hotchkiss, MD[5]

Blockade ofthe negative co-stimulatory molecules PD-1 and CTLA-4 improves survival in primary and secondary fungal sepsis

Katherine C Chang[1], Carey-Ann Burnham[2], Stephanie M Compton[1], David P Rasche[1], RichardJ Mazuski[1], Jacquelyn SMcDonough[1], Jacqueline Unsinger[1], Alan J Korman[3], Jonathan M Green[4] and Richard S Hotchkiss[1,4*]

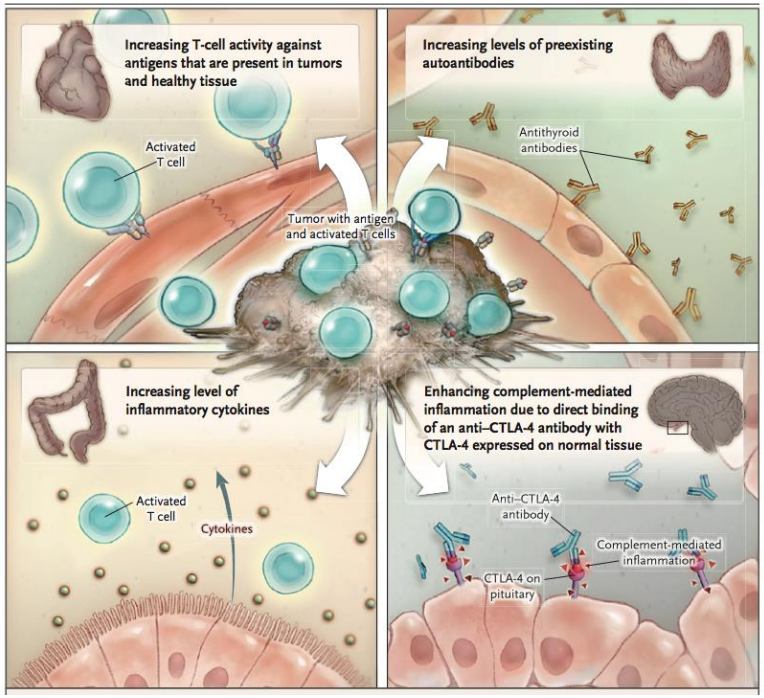
Les Dangers ?

Dan L. Longo, M.D., *Editor*

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

Michael A. Postow, M.D., Robert Sidlow, M.D., and Matthew D. Hellmann, M.D.

- **En oncologie :**



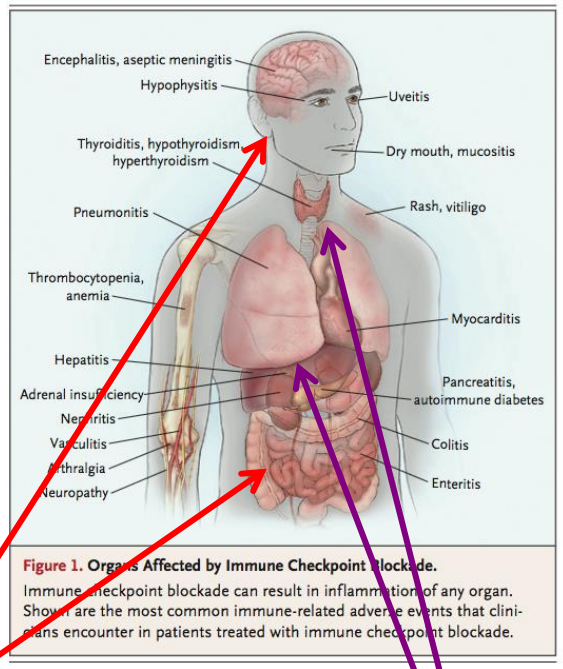


Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

Sepsis : Traitement court

CTLA4 + sévères

PD1

Conclusion (1) les questions non résolues ?

- **Impact du site de l'infection : étude sur « sepsis »**
- **La gestion des IRIS ?**
- **Immuno senescence accélérée ?**
- **Implication dans d'autres pathologies**
  - VIH (PD1)
  - Infection chronique (abcès/BK)
- **Quid des immunodéprimés (exclus des études)**

Conclusion (2) : L'immunothérapie idéale ?

- **Développement d'outils très prometteurs**
  - Traitement ciblé à la carte
  - Action ciblée
  - Effet réversible
- **Leurs place …**

Quel patient ?	Quelle Cibles ?	Critères d'évaluations ?	Sécurité ?
- Lymphopénie - HLA DR	- GM-CSF - IL7	- Infection II - Marqueur bio	- Oncologie - Traitement court
- PD1/PD1L - TNF/LPS	- PD1/PD1L - INF	- Def. Organes - Test fonctionnel	- IRIS ? - Durée action ?
- Transcriptomique	- MDSC - CARS T cell ?	- Evènements tardifs - Cardio-vasculaire	- Induction auto-I - Cardio vasculaire - Cancer