SOCIETE DE PHARMACIE DE LYON
Janvier 2022

Immunothérapie dans les infections sévères en réanimation choc septique et COVID-19

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Hospices Civils de Lyon

Flow Division
Immunology Department

Lyon 1

Prof. G. Monneret :

- Aucun conflit d'intérêt personnel
- Directeur EA 7426 (U. Lyon 1 / HCL / bioMérieux)

Any given life-threatening infection results, by definition, from an immunodeficiency, whether inherited or acquired

Casanova JL, Science 2007

Science AAAS

I. Physiopathologie du sepsis (infections sévères)

More than ever: septic syndromes still a serious a public health concern

2017 — World Health Organization

Recognizing Sepsis as a Global Health Priority — A WHO Resolution

Konrad Reinhart, M.D., Ron Daniels, M.D., Niranjan Kissoon, M.D., Flavia R. Machado, M.D., Ph.D., Raymond D. Schachter, L.L.B., and Simon Finfer, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

2020 (jan) **Globally, sepsis accounts for 11 million deaths / year (Rudd et al. Lancet)**

"By comparison, the World Health Organisation estimated that there were 9.6 million deaths from cancer in 2018".

THE LANCET

2021 COVID-19: it's all about sepsis

Jean-Louis Vincent*,1

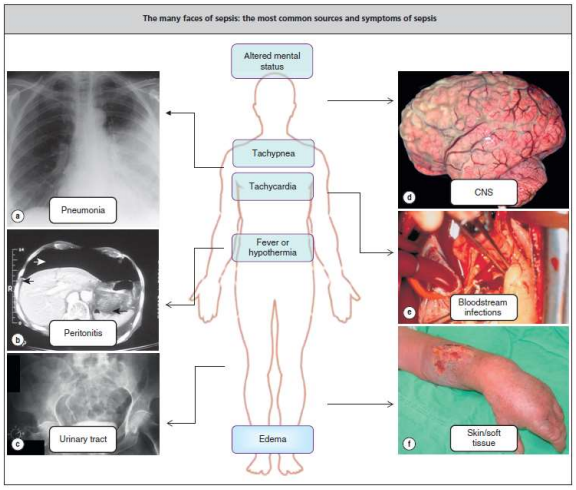
2,5 million deaths / year

Future MICROBIOLOGY

2021
- leading cause of death in ICU
- 28-day mortality: sepsis = 20 %, septic shock = 40 %

What is sepsis ?

Any type of germ: bacterial, viral or fungal
Any site : Pneumonia, gut, kidney, bloodstream infection
can lead to sepsis



Sepsis 2016 definition

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

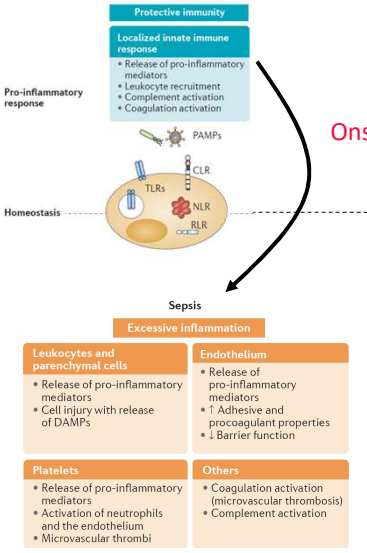
Sepsis
Life threatening organ dysnfunction caused by a dysregulated host response to infection
(*i.e,* one infection + one organ failure)

Septic shock
Sepsis + vasopressor therapy needed
(*i.e.*, cardiovascular failure)

JAMA The Journal of the American Medical Association

Singer et al., JAMA 2016

Pathophysiology - Inflammation is a balancing act: neither too much nor too little is desirable



Onset: germ(s) + site of infection + local inflammation

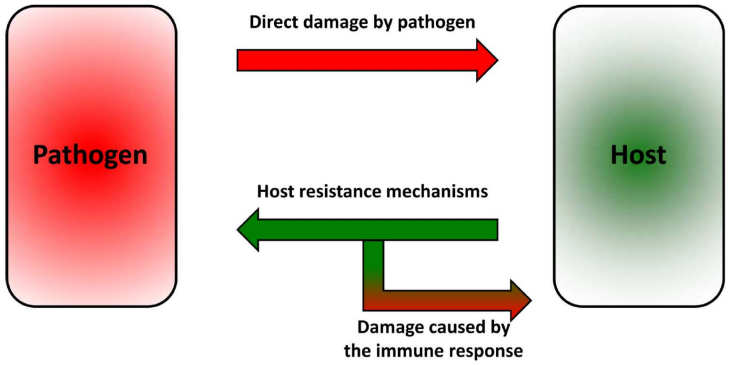
organ

systemic

Amplification ?
Lack of modulation ?
Bacterial – viral load ?

Pathophysiology : uncontrolled inflammatory response

Old paradigm for sepsis pathophysiology

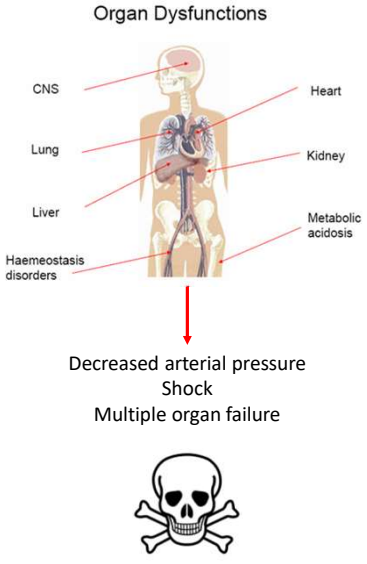


« collateral damage »

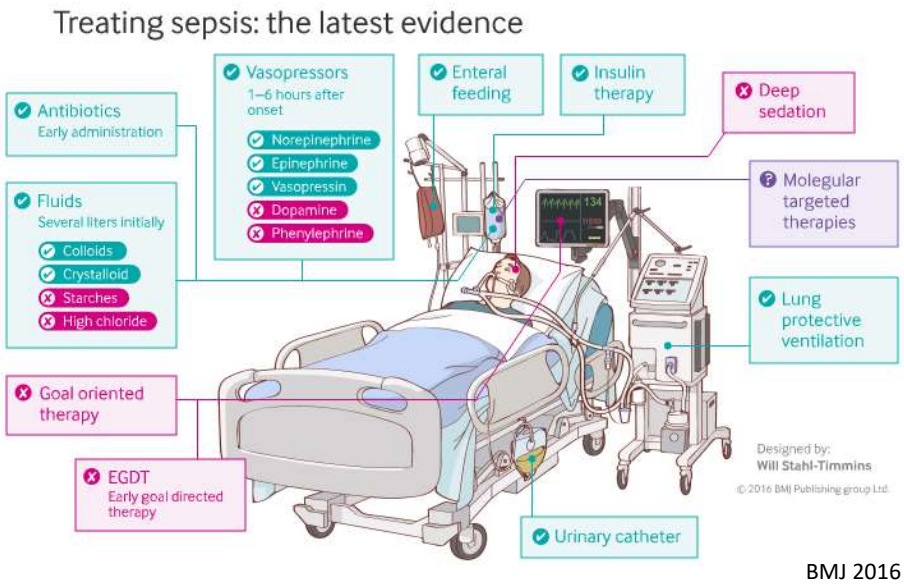
Adated from Medzhitov et al., Science 2012

Old paradigm for sepsis pathophysiology

Uncontrolled Inflammatory response →

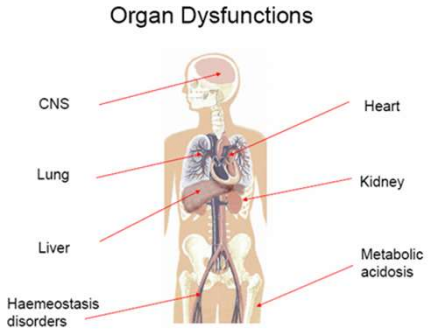


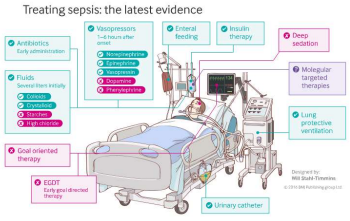
Early treatment
antibiotherapy + agressive vascular resuscitation (vasoactive agents + fluids)



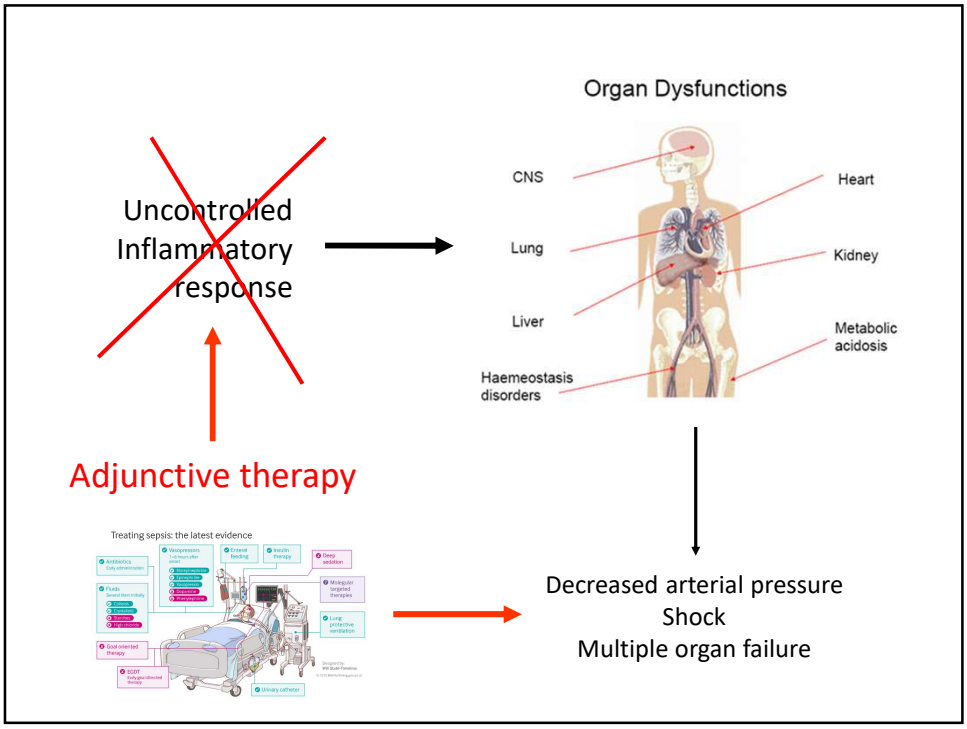
BMJ 2016

Uncontrolled Inflammatory response →





→ Decreased arterial pressure
Shock
Multiple organ failure

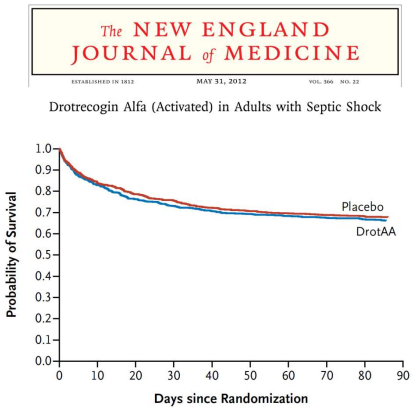


Failure of clinical trials testing anti-inflammatory therapies

Drug	Number of studies	Number of patients	Mortality (%) Placebo	Drug
Anti-endotoxine	4	2010	35	35
Anti-bradykinine	2	755	36	39
Anti-PAF	2	870	50	45
Anti-TNF	8	4132	41	40
R solubles TNF	2	688	38	40
AINS	3	514	40	37
Steroids	9	1267	35	39
(high doses)	...	...	...	...
...				
Total	33	12034	**38**	**38**

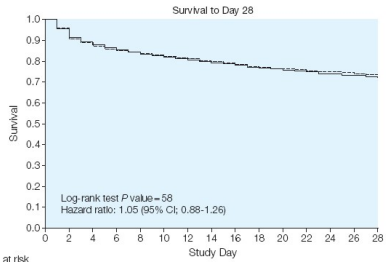
Zeni et al, Crit Care Med, 1997

40 years of failure in anti-inflammatory therapies



Ranieri et al. 2012

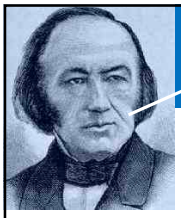
Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis
The ACCESS Randomized Trial



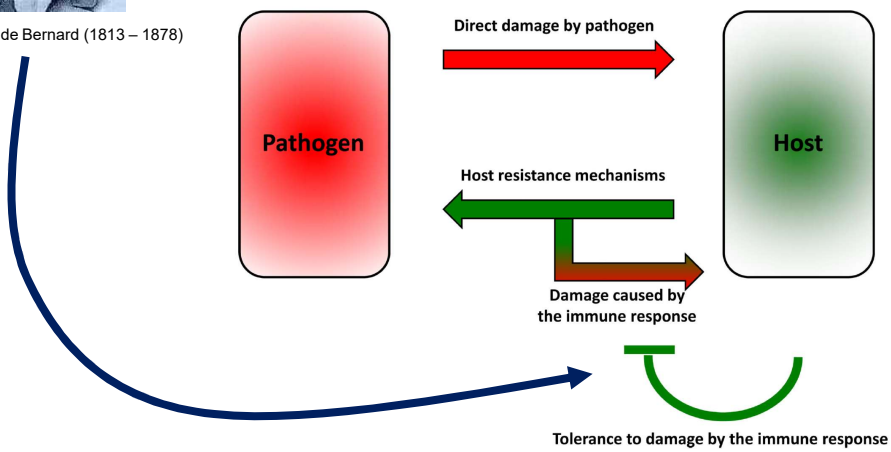
JAMA The Journal of the American Medical Association

Opal et al. 2013

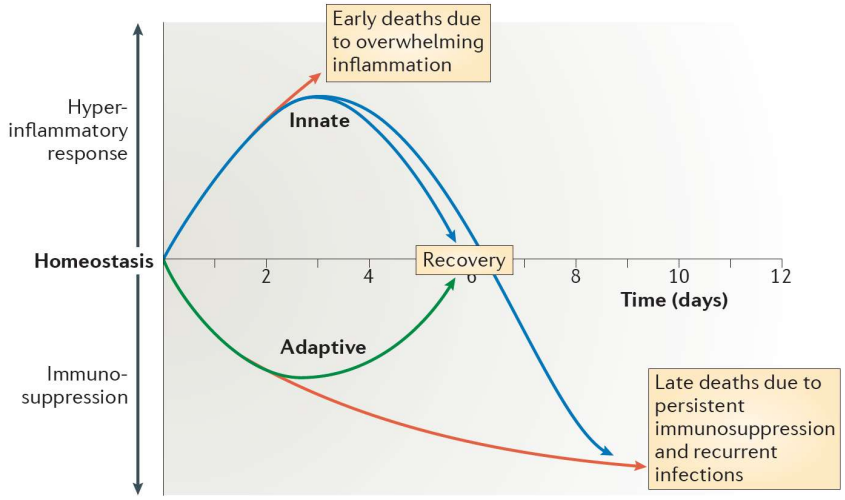
« Only homeostasis matters »



Claude Bernard (1813 – 1878)



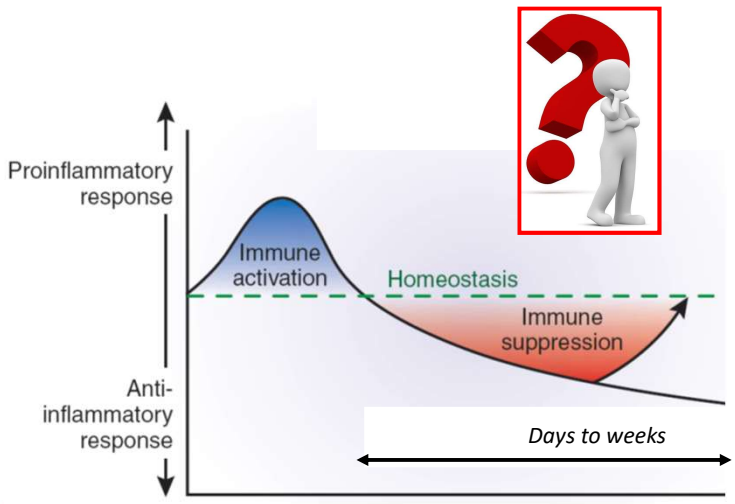
Pro- / anti-inflammatory balance in septic shock



nature REVIEWS IMMUNOLOGY

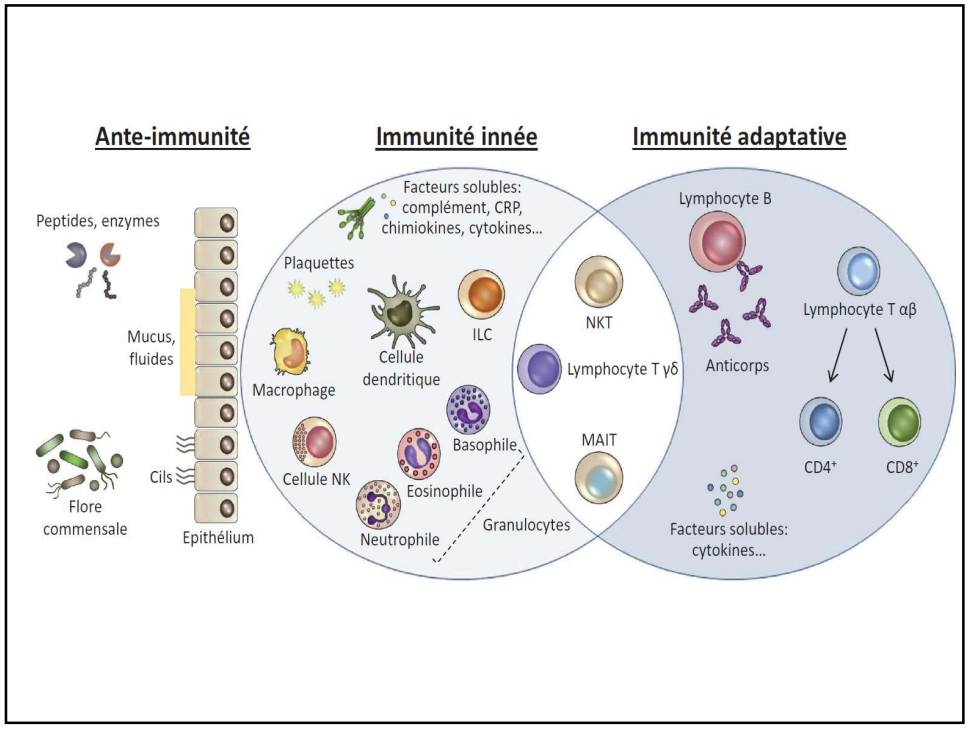
Hotchkiss, Monneret & Payen, 2013

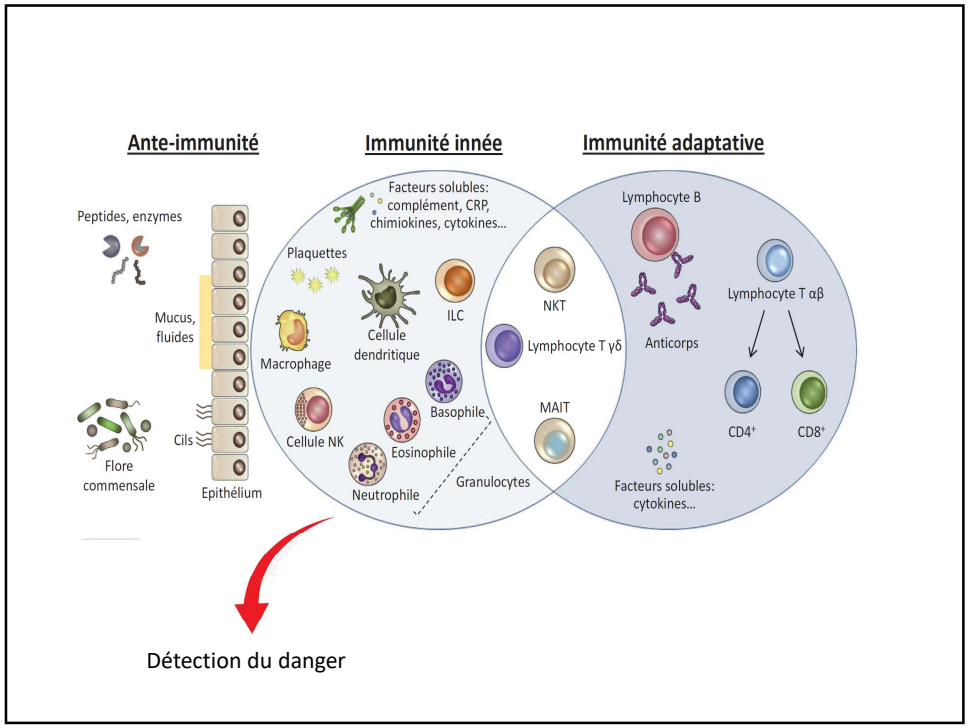
From exacerbated inflammation to immunosuppression in severely injured patients



nature medicine

Hotchkiss et al., 2009


Ante-immunité
Immunité innée
Immunité adaptative
Peptides, enzymes
Mucus, fluides
Flore commensale
Cils
Epithélium
Facteurs solubles: complément, CRP, chimiokines, cytokines...
Plaquettes
Macrophage
Cellule dendritique
ILC
Cellule NK
Basophile
Eosinophile
Neutrophile
Granulocytes
NKT
Lymphocyte T γδ
MAIT
Lymphocyte B
Anticorps
Lymphocyte T αβ
CD4+
CD8+
Facteurs solubles: cytokines...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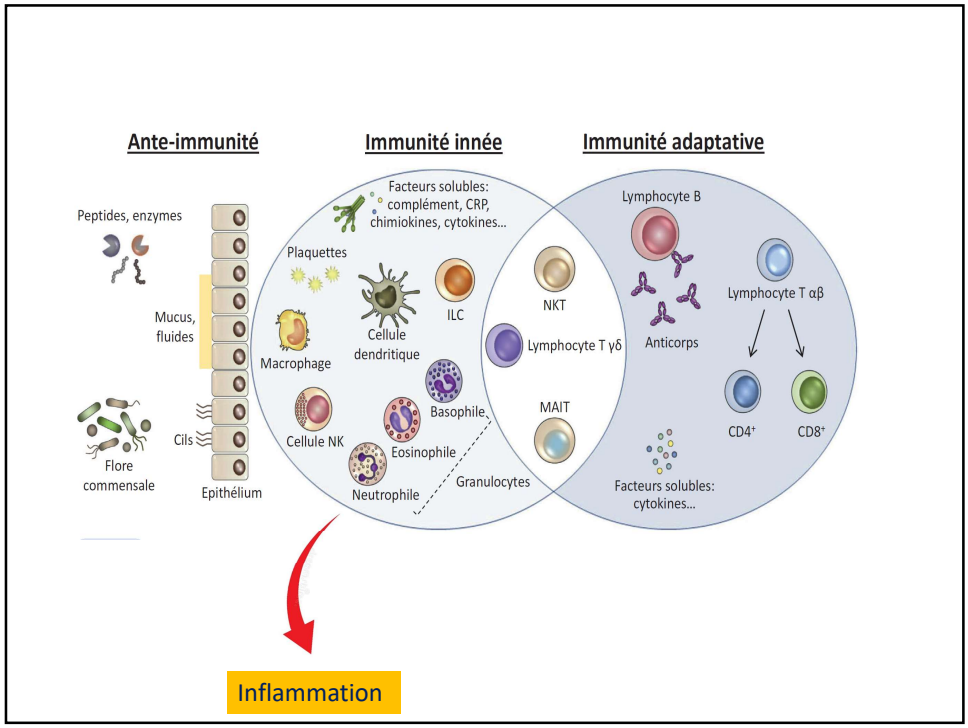
Lymphocyte T αβ
CD4+
CD8+
Facteurs solubles: cytokines...
Détection du danger


Ante-immunité
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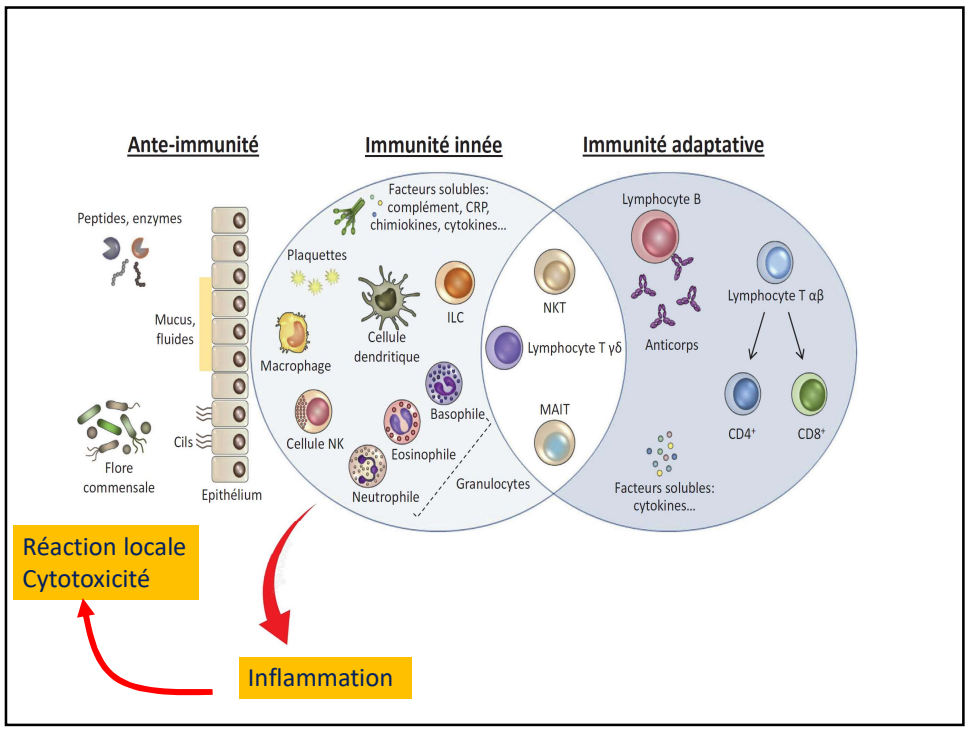
Lymphocyte B
Anticorps
Facteurs solubles: cytokines...
Lymphocyte T αβ
CD4+
CD8+
Inflammation


Ante-immunité
Immunité innée
Immunité adaptative
Peptides, enzymes
Mucus, fluides
Cils
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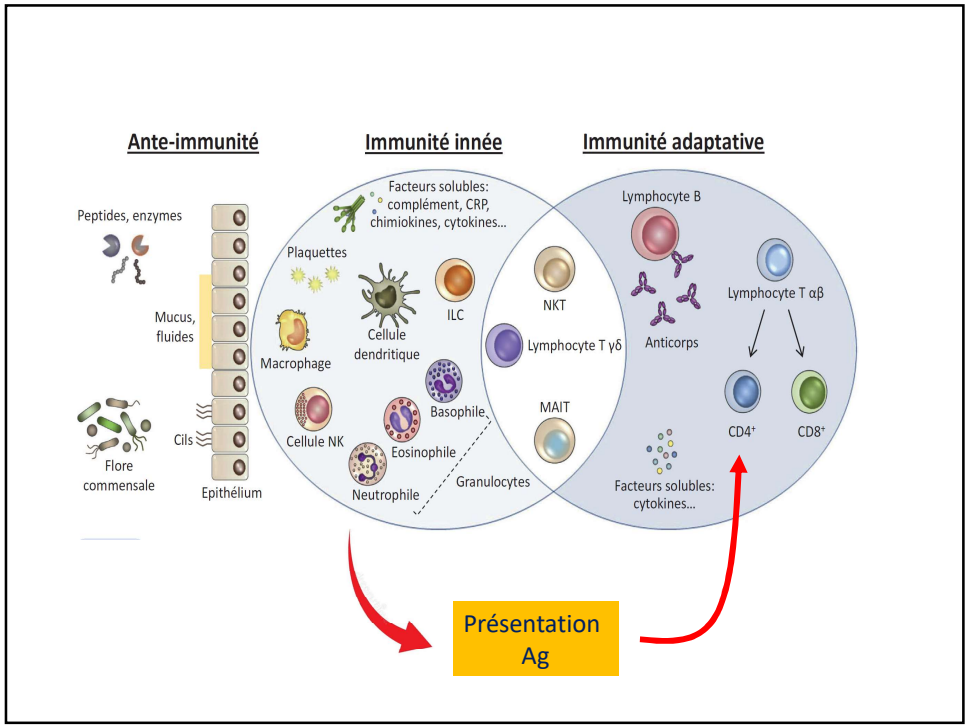
NKT
Lymphocyte T γδ
MAIT
Lymphocyte B
Anticorps
Facteurs solubles: cytokines...
Lymphocyte T αβ
CD4+
CD8+
Réaction locale
Cytotoxicité
Inflammation


Ante-immunité
Immunité innée
Immunité adaptative
Peptides, enzymes
Mucus, fluides
Flore commensale
Cils
Epithélium
Facteurs solubles: complément, CRP, chimiokines, cytokines...
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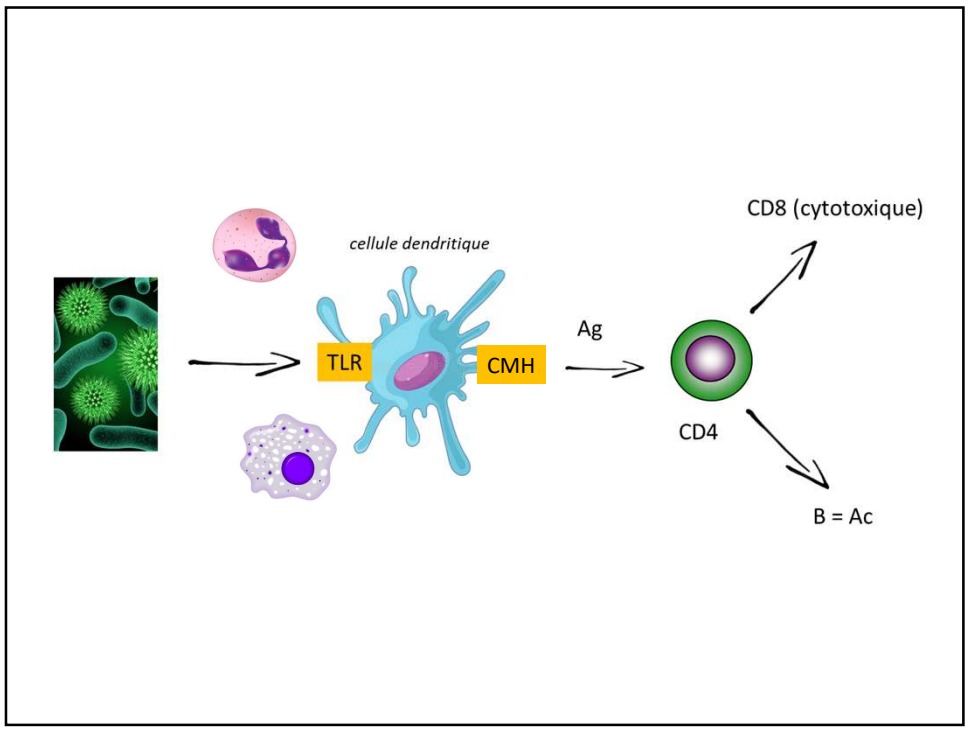
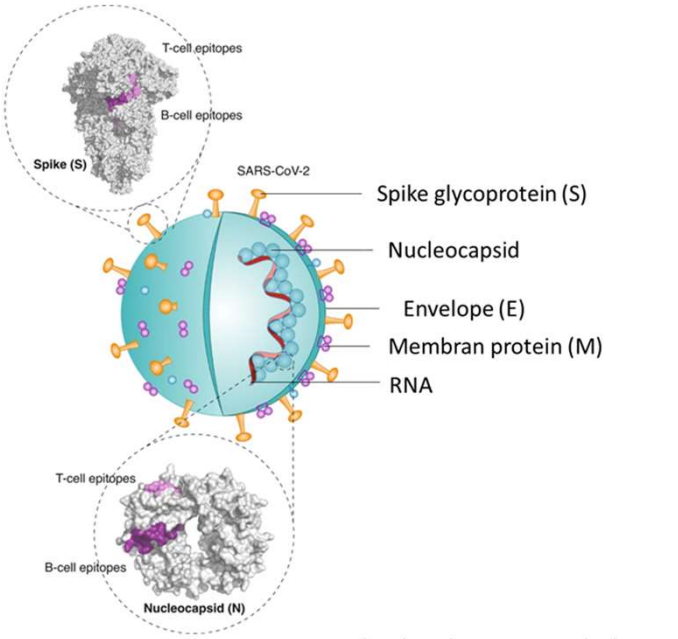
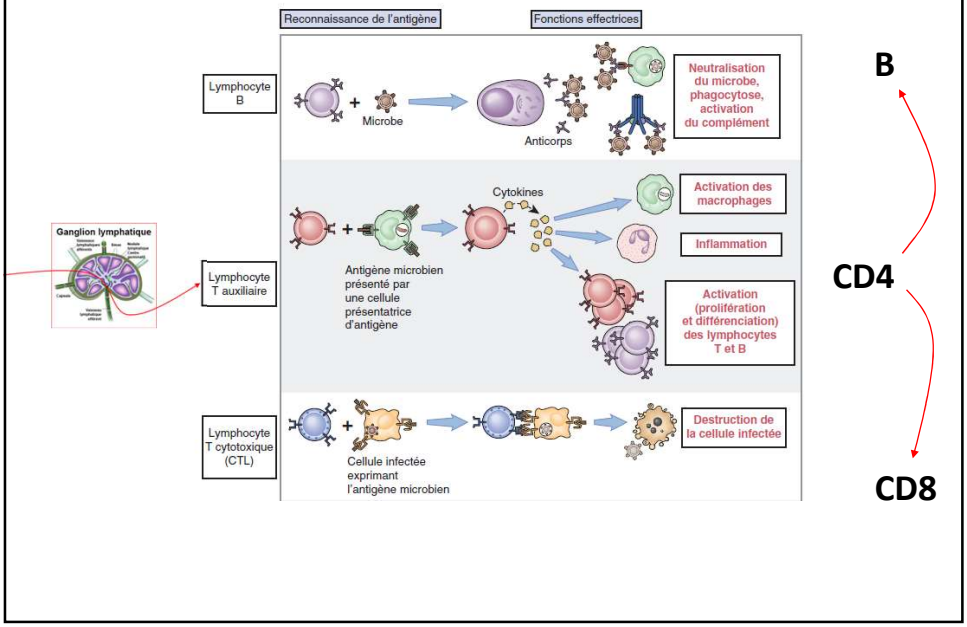
NKT
Lymphocyte T γδ
MAIT
Lymphocyte B
Anticorps
Lymphocyte T αβ
CD4+
CD8+
Facteurs solubles: cytokines...
Présentation Ag


cellule dendritique
TLR
CMH
Ag
CD8 (cytotoxique)
CD4
B = Ac


T-cell epitopes
B-cell epitopes
Spike (S)
SARS-CoV-2
Spike glycoprotein (S)
Nucleocapsid
Envelope (E)
Membran protein (M)
RNA
T-cell epitopes
B-cell epitopes
Nucleocapsid (N)
Florindo et al. Nature Nanotechnology 202

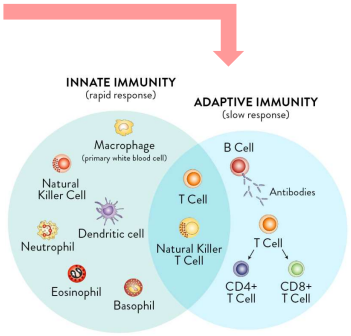

Reconnaissance de l'antigène
Fonctions effectrices
Lymphocyte B
Microbe
Anticorps
Neutralisation du microbe, phagocytose, activation du complément
Ganglion lymphatique
Lymphocyte T auxiliaire
Cytokines
Activation des macrophages
Inflammation
Antigène microbien présenté par une cellule présentatrice d'antigène
Activation (prolifération et différenciation) des lymphocytes T et B
Lymphocyte T cytotoxique (CTL)
Cellule infectée exprimant l'antigène microbien
Destruction de la cellule infectée
B
CD4
CD8

Main mechanisms sustaining immune dysfunctions in sepsis

Table 1

Sepsis-induced immune dysfunctions: pathophysiology at a glance

Mechanisms	Features of sepsis-induced immune alterations
Endotoxin tolerance	↓ pro-inflammatory ↑ anti-inflammatory cytokine production ↓ Ag presentation capacity
Apoptosis	↓ cell number Cell anergy
Energetic failure	Cell anergy Apoptosis Mitochondrial dysfunction
Anti-inflammatory mediators	↓ activating co-receptor expressions ↑ inhibitory co-receptor expressions Cell anergy Endotoxin tolerance
Epigenetic regulation	↓ pro-inflammatory gene expressions Cellular reprogramming
Central and endocrine Regulations	↓ pro-inflammatory cytokine production

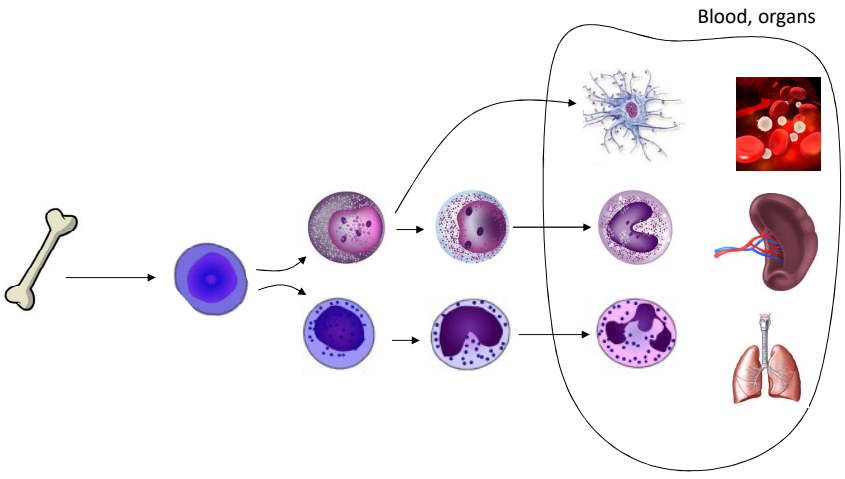


Are ICU injured patients really immunosuppressed ?

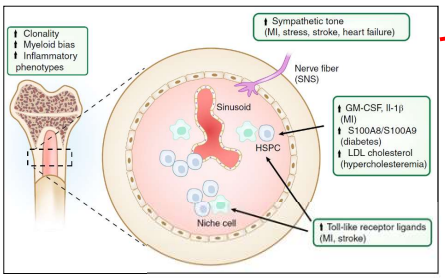
Current Opinion in Immunology *Venet et al.,2013*

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Special Issue: *The Year in Immunology*
REVIEW

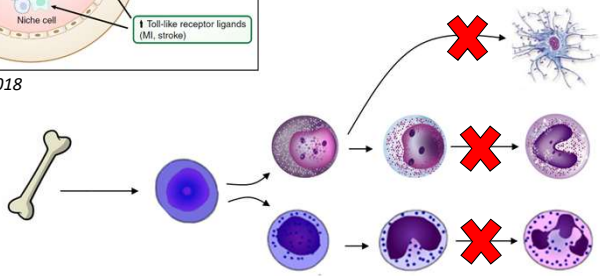
Myeloid cells in sepsis-acquired immunodeficiency



Venet et al., 2020



Nahrendorf Nat Med 2018



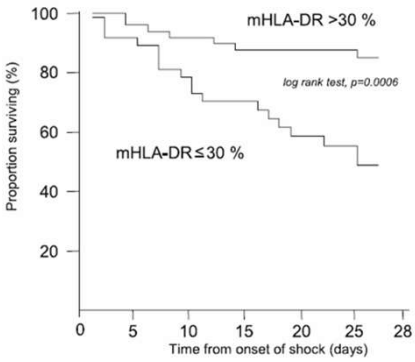
Immunosuppressive properties

Immature neutrophils
MDSC
Deactivated monocytes

Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock

ICM INTENSIVE CARE MEDICINE

Survival curves stratified on mHLA-DR at 30 % at days 3-4 (n = 120 patients)



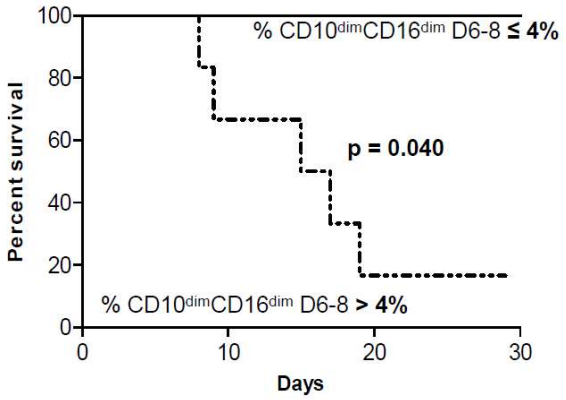
Multivariate analysis : mHLA-DR is an independent predictor of mortality (OR = 9) (after adjustment for usual clinical confounders : SAPS II, SOFA, comorbidities…)

Monneret et al., 2006

Marked alterations of neutrophil functions during sepsis-induced immunosuppression

JLB

At day 7, persitence of elevated % of immature neutrophils
Is associated with 28-day mortality



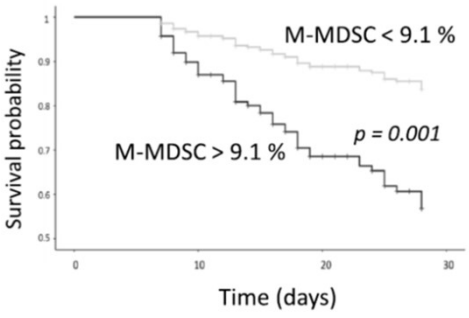
Demaret et al., 2015, J Leuko Biol

Delayed persistence of elevated monocytic MDSC associates with deleterious outcomes in septic shock: a retrospective cohort study

CRITICAL CARE

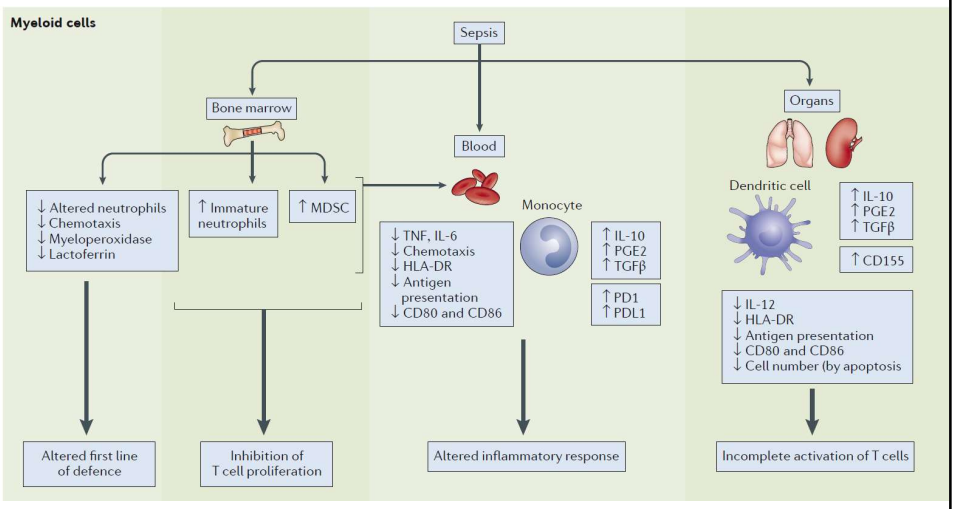
At day 7 (n = 301 septic shock)

↑ MDSC = ↑ infections ↑ mortality



Waeckel et al., 2021

Myeloid cells (summary)



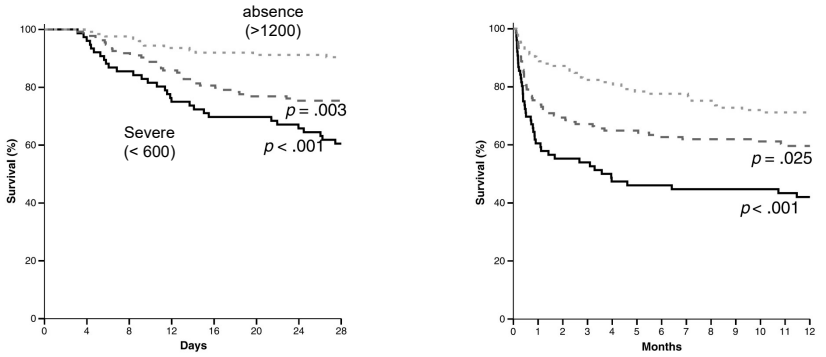
nature REVIEWS

Venet & Monneret, 2018

PERSISTENT LYMPHOPENIA AFTER DIAGNOSIS OF SEPSIS PREDICTS MORTALITY

Anne M. Drewry,* Navdeep Samra,† Lee P. Skrupky,‡ Brian M. Fuller,*§ Stephanie M. Compton,* and Richard S. Hotchkiss*†

=> Day 4 total lymphocyte count



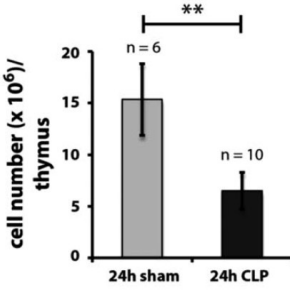
SHOCK, Vol. 42, No. 5, pp. 383–391, 2014

Thymus

APOPTOTIC DIMINUTION OF IMMATURE SINGLE AND DOUBLE POSITIVE THYMOCYTE SUBPOPULATIONS CONTRIBUTES TO THYMUS INVOLUTION DURING MURINE POLYMICROBIAL SEPSIS

Christoph Netzer,* Tilo Knape,† Laura Kuchler,* Andreas Weigert,* Kai Zacharowski,‡ Waltraud Pfeilschifter,§ Gregory Sempowski,¶ Michael J. Parnham,† Bernhard Brüne,*† and Andreas von Knethen*†

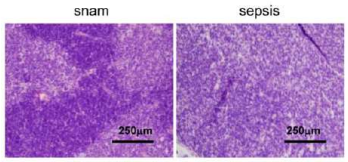
SHOCK, Vol. 48, No. 2, pp. 215–226, 2017

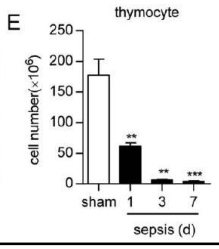


Sepsis-Induced Thymic Atrophy Is Associated with Defects in Early Lymphopoiesis

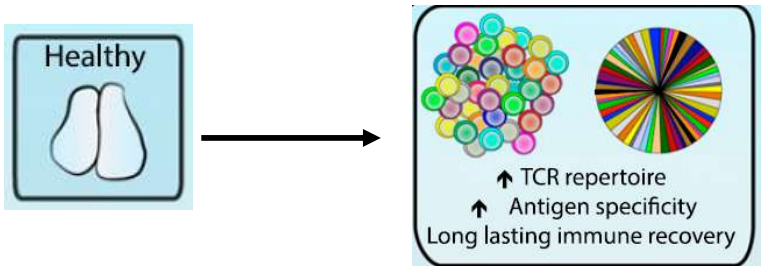
STEM CELLS 2016;34:2902–2915

YAXIAN KONG,[a,b] YAJIE LI,[a,b] WEIMEI ZHANG,[a,b] SHAOXIN YUAN,[a,b] RENÉ WINKLER,[c] ULRIKE KRÖHNERT,[c] JUNYAN HAN,[a,b] TAO LIN,[a,b] YU ZHOU,[d] PENG MIAO,[e] BEIBEI WANG,[a,b] JIANPING ZHANG,[a,b] ZHENGYA YU,[e] YU ZHANG,[d] CHRISTIAN KOSAN,[c] HUI ZENG[a,b]

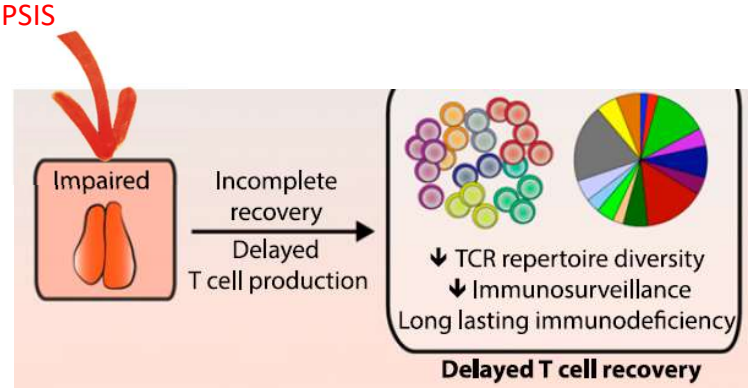




STEM CELLS



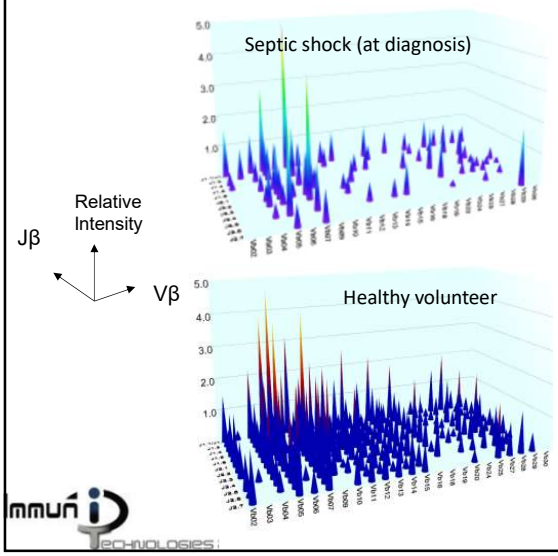
SEPSIS

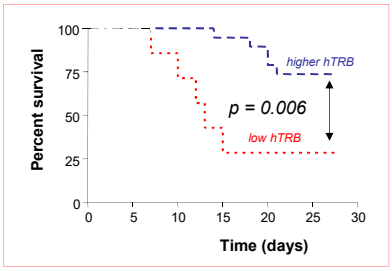


Adapted from Chaudhry HS, J Immunol 2017

Marked decreased TCR diversity independently of lymphopenia

(hTRB VJ combinatorial diversity assessed by qRT-PCR)





Venet et al., Crit Care Medicine (2013)

Le Monde

MÉDECINE Partage

Le Nobel de médecine sacre la percée de l'immunothérapie du cancer

Le Japonais Tasuku Honjo et l'Américain James Allison ont été distingués par l'académie du Karolinska Institute pour leurs travaux sur la régulation de la réponse immunitaire, qui ont abouti à la mise au point de traitements antitumoraux à l'efficacité inédite.

Par Sandrine Cabut · Publié le 01 octobre 2018 à 19h08 - Mis à jour le 02 octobre 2018 à 09h23

Lecture 5 min.

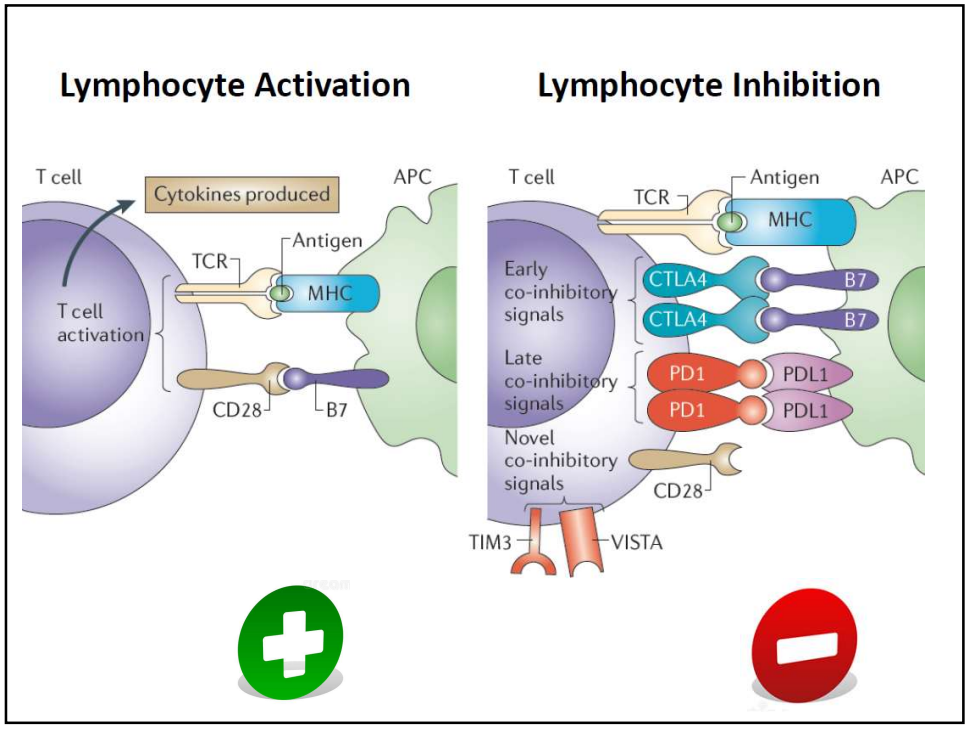
Article réservé aux abonnés

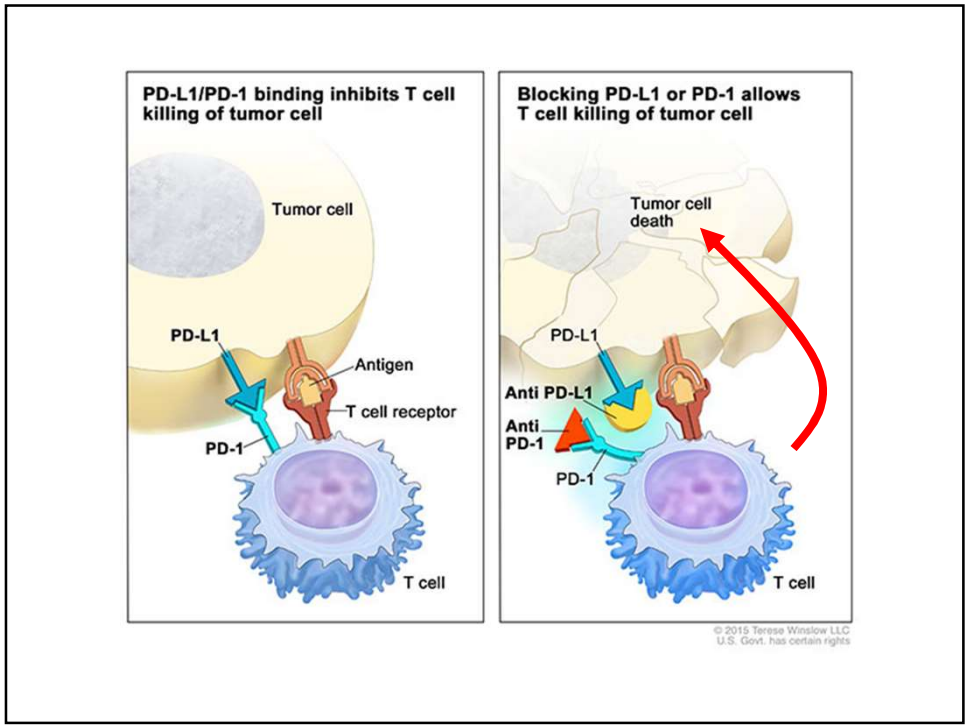
Honjo (PD-1)

Tasuku Honjo, à Kyoto et James Allison, à New-York, le 1er octobre. NOBUKI ITO /

Allison (CTLA-4)

Oct 2018


Lymphocyte Activation
Lymphocyte Inhibition
T cell
Cytokines produced
APC
T cell activation
TCR
Antigen
MHC
CD28
B7
T cell
TCR
Antigen
APC
MHC
Early co-inhibitory signals
CTLA4
B7
CTLA4
B7
Late co-inhibitory signals
PD1
PDL1
PD1
PDL1
Novel co-inhibitory signals
CD28
TIM3
VISTA


PD-L1/PD-1 binding inhibits T cell killing of tumor cell
Tumor cell
PD-L1
Antigen
T cell receptor
PD-1
T cell
Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Tumor cell death
PD-L1
Anti PD-L1
Anti PD-1
PD-1
T cell
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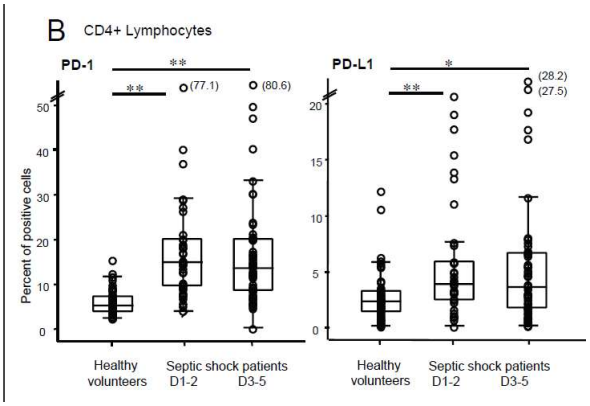
Programmed death-1 levels correlate with increased mortality, nosocomial infection and immune dysfunctions in septic shock patients

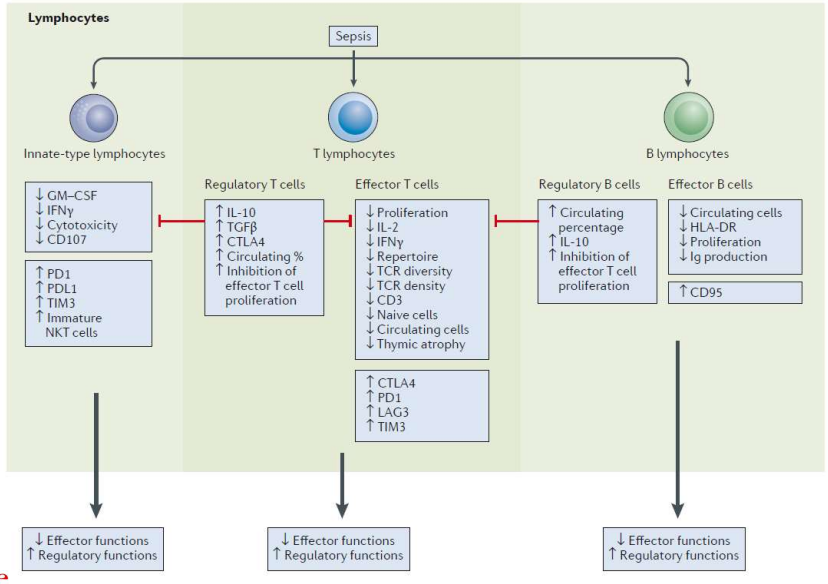
CRITICAL CARE 2011

Caroline Guignant[1], Alain Lepape[2], Xin Huang[3], Hakim Kherouf[1], Laure Denis[4], Françoise Poitevin[1], Christophe Malcus[1], Aurélie Chéron[5], Bernard Allaouchiche[5], François Gueyffier[6], Alfred Ayala[3], Guillaume Monneret[1*†] and Fabienne Venet[1†]



Associated with:
- 28-day mortality
- Nosocomial infection
- Decreased proliferation

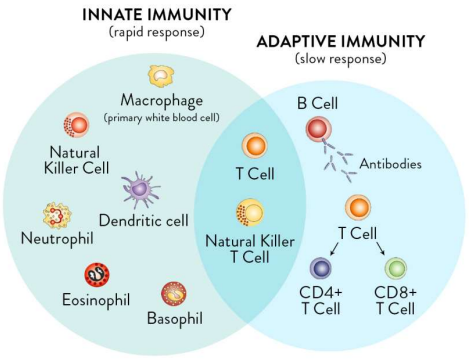
Lymphoid cells (summary)

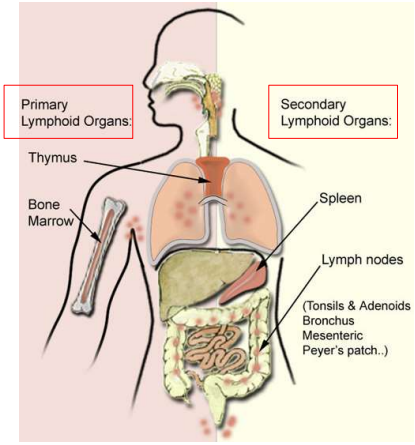


nature REVIEWS

Venet & Monneret, 2018

Summary





Summary

Immunodépression dans le sepsis principales caractéristiques

Immunité innée
- Neutrophiles immatures & MDSC = ↑
- % Monocyte désactivés = ↑
- Capacité présentation Ag : ↓

Immunité adaptative
- Lymphopénie
- Molécules inhibitrices PD-1 = ↑
- Répertoire Lymphocytaire : ↓

Soins courants
Immuno - HCL

Conséquences de l'mmunodépression

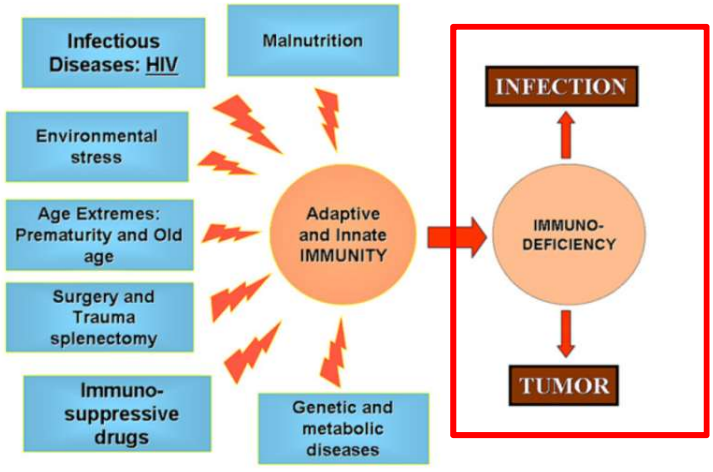


FIG 1. Extrinsic factors leading to defects of immune function.

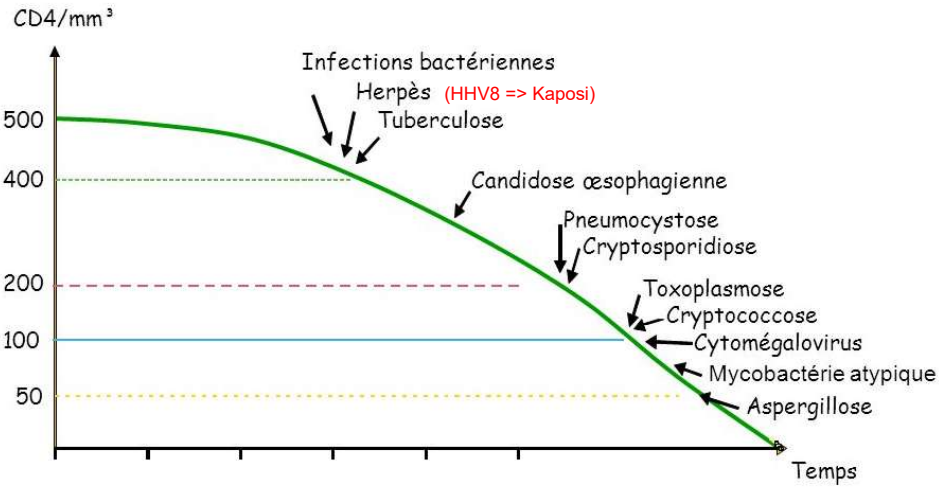
Chinen and Shearer, J Allergy Clin Immunol 2010

Virus de l'Immunodéficience Humaine

DECOUVERTE

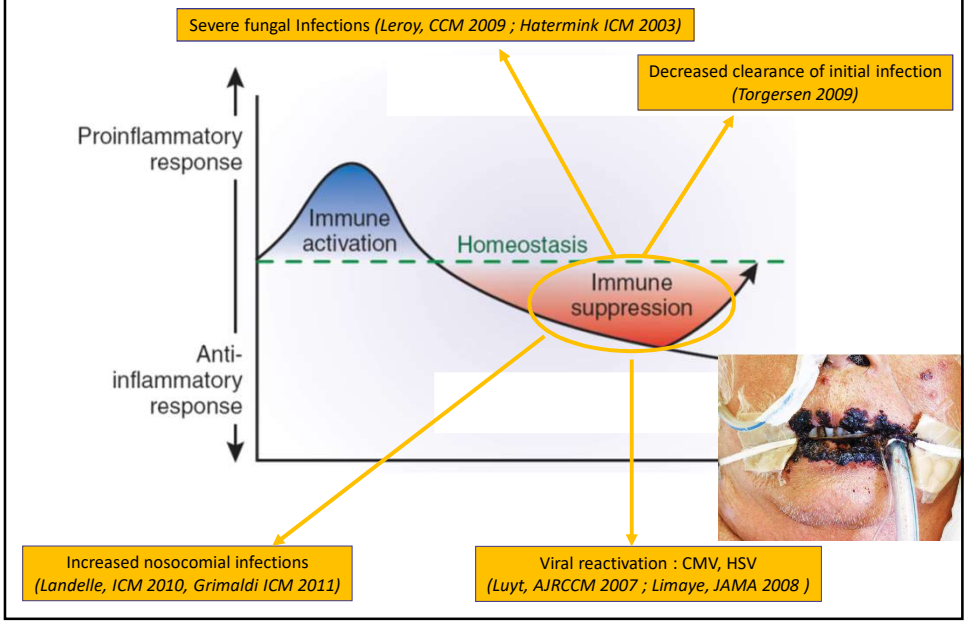
Juin 1981, à Los Angeles et New York:
Epidémie de 1er cas d'infections opportunistes + sarcomes de Kaposi = SIDA

Survenue des complications infectieuses au cours du SIDA en fonction de la chute progressive du nombre de lymphocytes CD4 au cours du temps

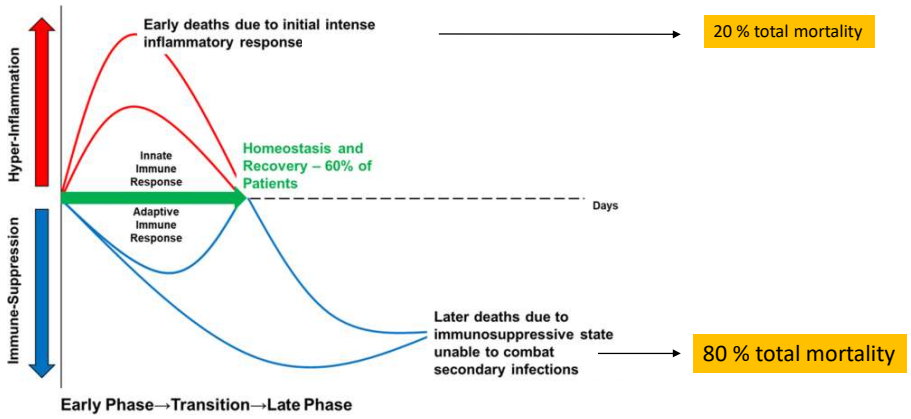


Girard et al., Doin SIDA 1996

Increased secondary / nosocomial infections = increased mortality



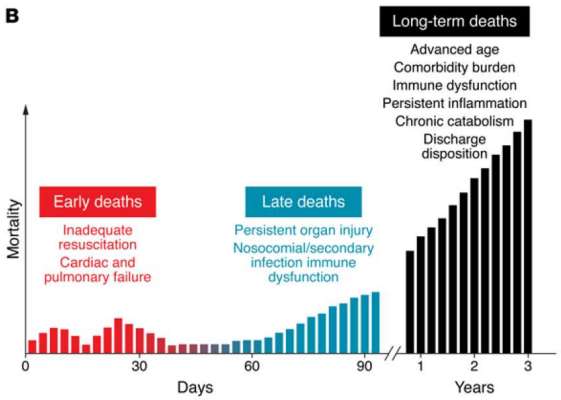
Pro- / anti-inflammatory balance in septic shock



Brady et al., 2020

Intensive Care Medicine Experimental

Persistent immunosuppression could be associated with late mortality (years)?



2 years mortality : + 20 %
30 % infection (first cause)

Sepsis survivors :
30 % 30-day rehospitalisation
60 % 1-year rehospitalisation
First cause : sepsis
Significant unresolved infection

Delano and ward, J Clin Invest 2016, Shankar-Hari and Rubenfeld, Curr Infect Dis Resp 2016, Kennelly and martin-Loevhes, Ann Transl Med 2016, Kaur and Levy, Ann Transl Med 2016, Prescott et al., BMJ 2016, Sun et al., CCM 2016, Pavon et al., CCM 2014, Wabng et al BMJ 2014

Assessment of sepsis-induced immunosuppression at ICU discharge and 6 months after ICU discharge

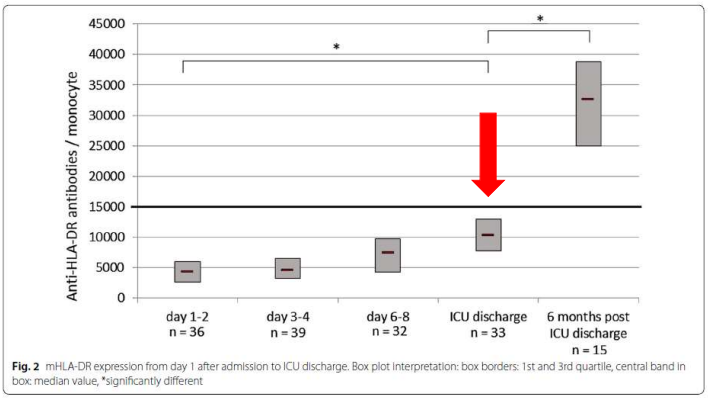


Fig. 2 mHLA-DR expression from day 1 after admission to ICU discharge. Box plot interpretation: box borders: 1st and 3rd quartile, central band in box: median value, *significantly different

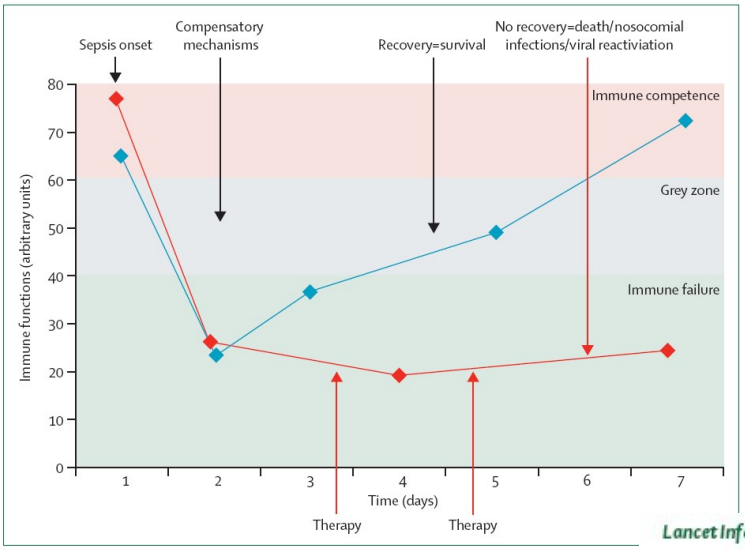
Median discharge = 11 days

Annals of Intensive Care

Zorio *et al. Ann. Intensive Care (2017) 7:80*

Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach

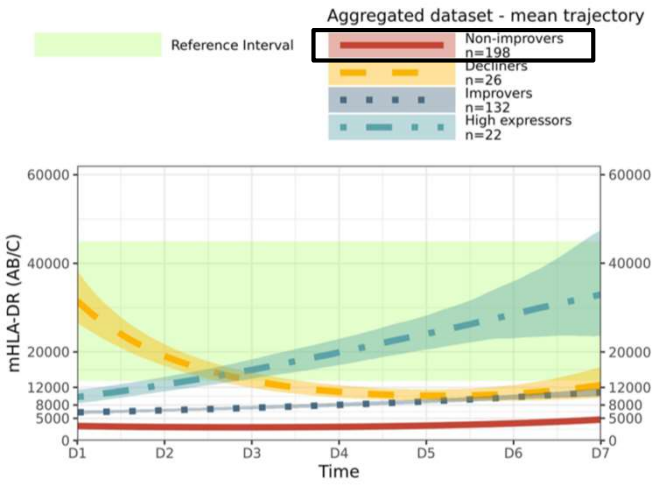
Richard S Hotchkiss. Guillaume Monneret. Didier Payen



Lancet Infect Dis 2013; 13: 260–68

Monocyte Trajectories Endotypes Are Associated With Worsening in Septic Patients

frontiers in Immunology



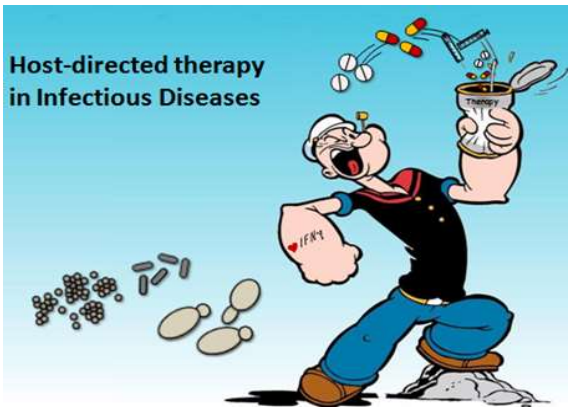
0 % infection
9 % mortality

19 % infection
28 % mortality

n = 378 ICU patients

Bodinier et al., 2021

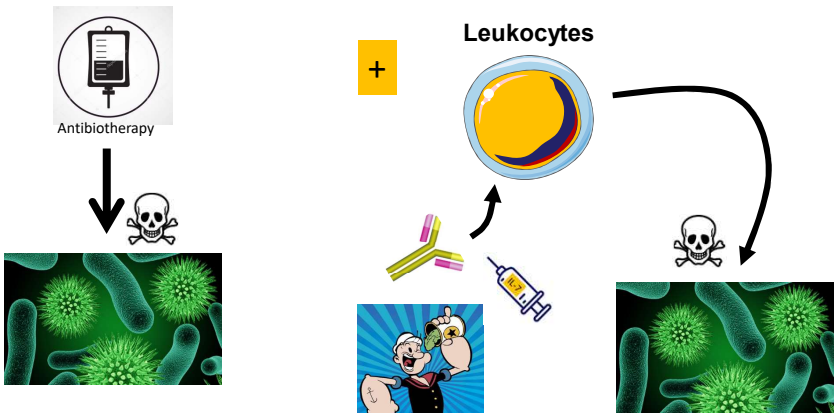
II. Immunothérapie des infection sévères



Principles of immunotherapy in sepsis

Historical Concept : Targeting germs	New Concept: Targeting Immune Cells

rejuvenate / stimulate immune cells



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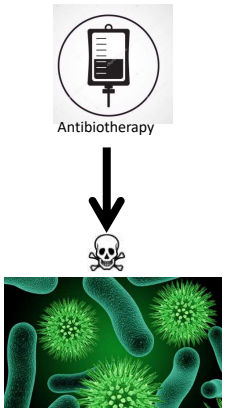

Principles of immunotherapy in sepsis

Historical Concept : Targeting germs

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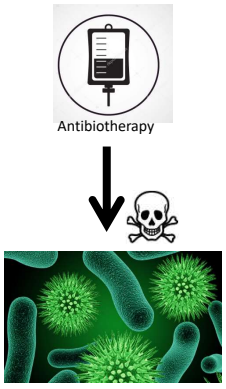
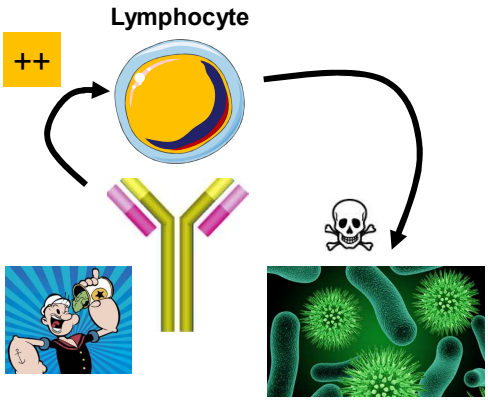
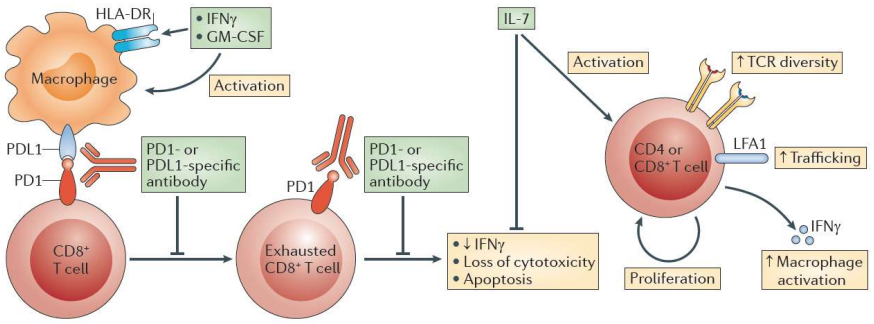




Immunotherapy in sepsis (as in cancer)

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

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



nature REVIEWS IMMUNOLOGY 2013

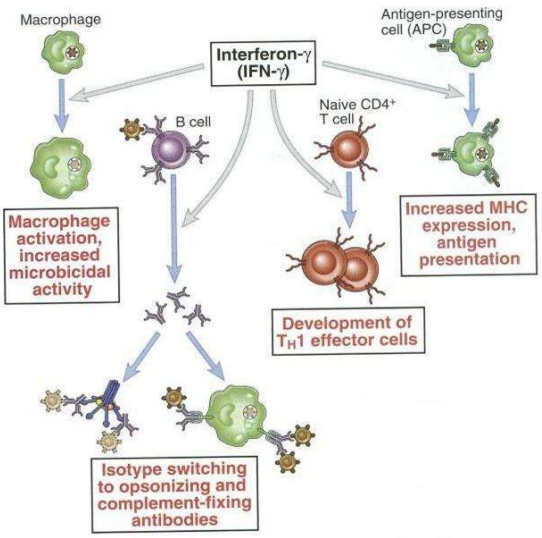
Compelling preclinical results in sepsis:

- Improves bacterial clearance and mortality in mice
  (Hotchkiss et al., 2008, 2011, 2013, 2015)
- Restores immune functions ex-vivo in human cells
  (Venet et al., 2012, 2017)

Non randomized trials and case reports (successful):

- *Docke et al., Narture Med 1997 IFNg*
- *Nakos et al., CCM 2002 (nosocomial infections in trauma) IFNg*
- *Luckasewicz et al., CCM 2009 (nosocomial) IFNg*
- *Schefold et al., AJRCCM 2009 (septic shock) GM-CSF*
- *Hall et al., Intensive Care Med (pediatric MOF) GM-CSF*
- *Delsing et al, BMC Infectious Diseases 2014 (fungal infections) IFNg*
- *Nalos et al., AJRCCM 2012 (staph sepsis) IFNg*
- *Mezidi et al., Minerva Anesth 2014 (fungal infection) IFNg*

1. INTERFERON - γ (IMUKIN)



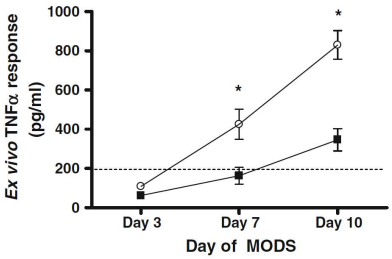
Docke WD et al. Nat Med. 1997;3:678-81
Monocyte deactivation in septic patients: restoration by IFN-gamma treatment

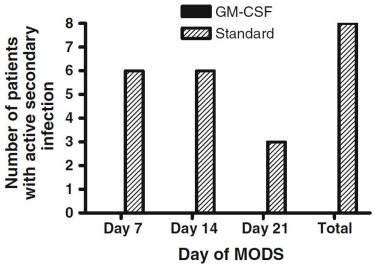
9 patients severe sepsis		26 patients severe sepsis
↓		↓
HLA-DR < 30 % (2 consecutive days)	*Non-randomized*	HLA-DR < 30 % (2 consecutive days)
↓		↓
Interferon-gamma		
Mortality 33 %		***Mortality 58 %***

nature medicine

Mark W. Hall
Nina L. Knatz
Carol Vetterly
Steven Tomarello
Mark D. Wewers
Hans Dieter Volk
Joseph A. Carcillo

Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome





Absence of nosocomial Infections on GM-CSF

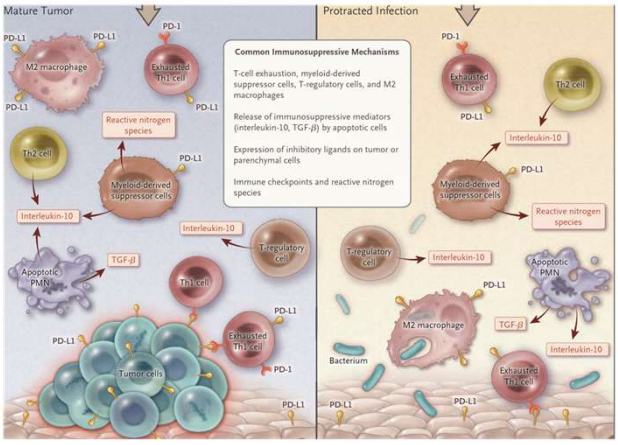
Intensive Care Med (2011) 37:525–532

2. Anti-PD-(L)1

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Parallels between Cancer and Infectious Disease

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



2016

Le Monde

MÉDECINE Partage

Le Nobel de médecine sacre la percée de l'immunothérapie du cancer

Le Japonais Tasuku Honjo et l'Américain James Allison ont été distingués par l'académie du Karolinska Institute pour leurs travaux sur la régulation de la réponse immunitaire, qui ont abouti à la mise au point de traitements antitumoraux à l'efficacité inédite.

Par Sandrine Cabut · Publié le 01 octobre 2018 à 19h08 - Mis à jour le 02 octobre 2018 à 09h23

Lecture 5 min.

Article réservé aux abonnés

Honjo (PD-1)

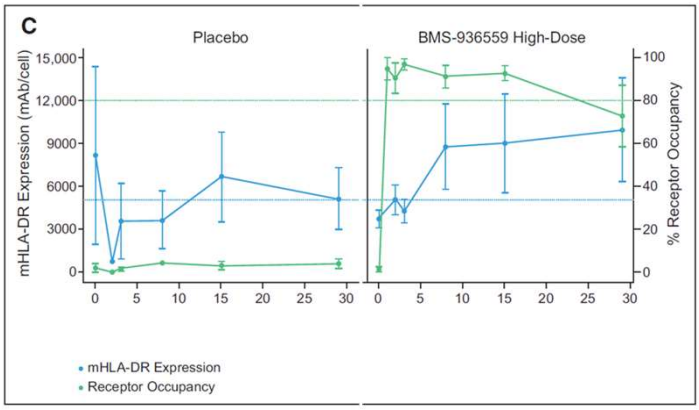
Allison (CTLA-4)

Tasuku Honjo, à Kyoto et James Allison, à New-York, le 1er octobre. NOBUKI ITO /

Oct 2018

Immune Checkpoint Inhibition in Sepsis: A Phase 1b Randomized, Placebo-Controlled, Single Ascending Dose Study of Antiprogrammed Cell Death-Ligand 1 Antibody (BMS-936559)*

Critical Care Medicine



Phase 1b, prospective, randomized, double-blind, placebo-controlled, dose escalation, multicenter study
Septic patients + immunusuppression (ALC < 1.1 G/L)
20 anti-PDL1 + 4 Placebo

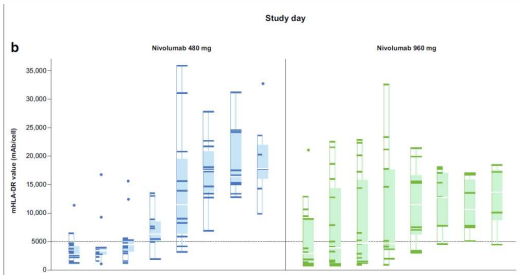
Hotchkiss et al., 2019

Immune checkpoint inhibition in sepsis: a Phase 1b randomized study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of nivolumab

Intensive Care Med (2019) 45:1360–1371

Take-home message

There were no safety concerns reported with nivolumab in an ICU-bound sepsis population at high risk for mortality and no indication of a 'cytokine storm'; findings were consistent with those of the anti-PD-L1, BMS-936559, in participants with sepsis-induced immuno-suppression. Further efficacy and safety studies are needed to assess the potential of checkpoint inhibitors as a treatment for sepsis.

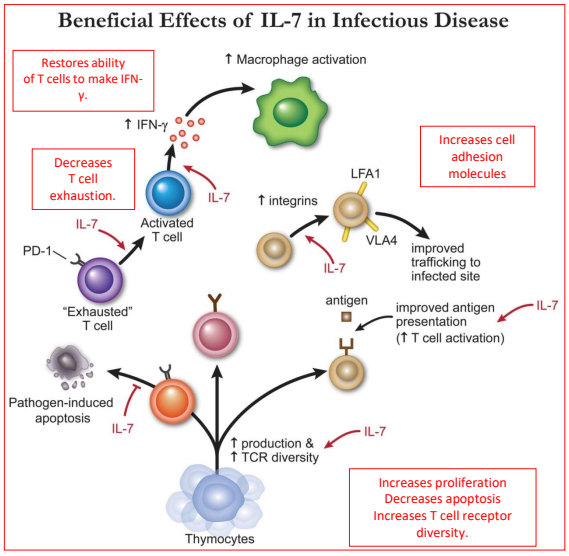


Hotchkiss et al.

3. IL-7

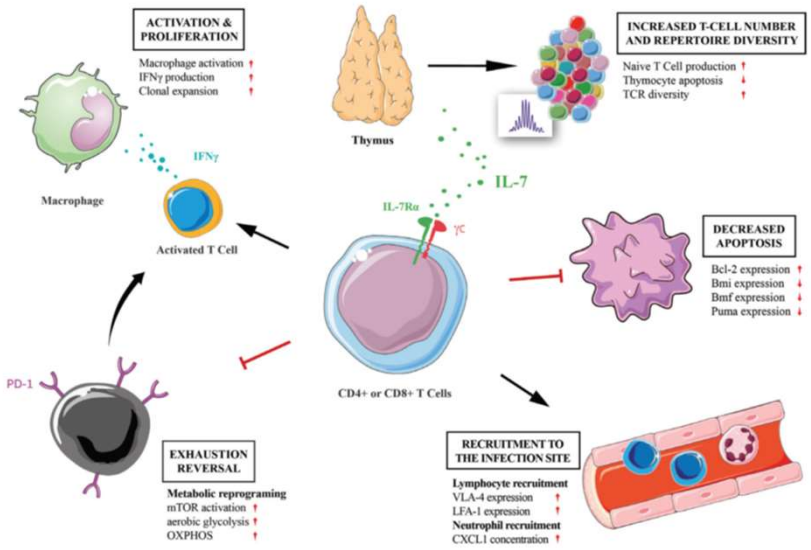
IL-7 acts at multiple levels to improve functionality of CD4 and CD8 T cells and secondarily adaptive immunity.

IL-7 offers a new approach to infectious disease.



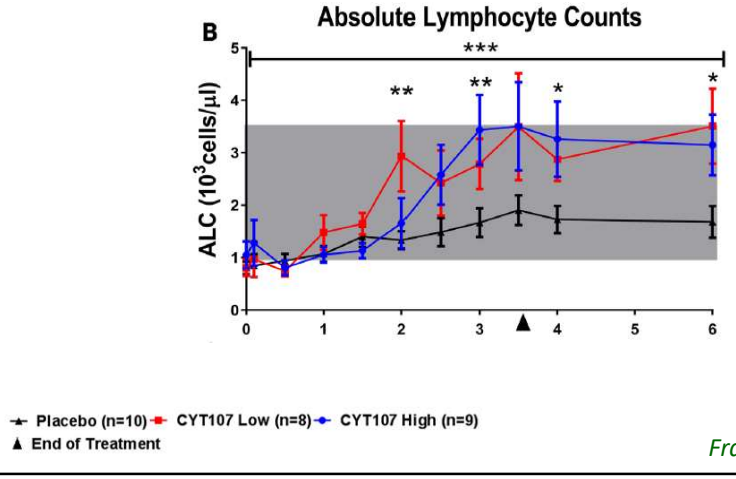
Trends in Molecular Medicine, April 2014, Vol. 20, No. 4

Interleukin-7 (essais en cours)



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

JCI insight

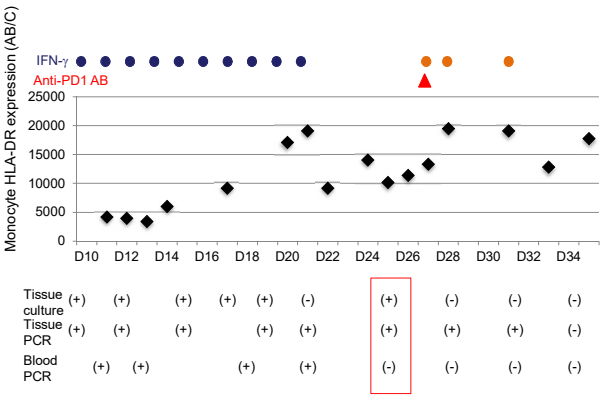


François et al., 2018

Examples from our routine practice

Nivolumab and Interferon-γ rescue therapy to control invasive mucormycosis after necrotising fasciitis and septic shock

Immumonitoring showed severe lymphopenia and very low mHLA-DR expression
=> severe immunosuppression



Nivolumab plus interferon-γ in the treatment of intractable mucormycosis

Acquired immunosuppression is an important complication of major trauma and might contribute to the development of severe fungal infections in these patients. Here, we describe a patient with extensive abdominal mucormycosis unresponsive to conventional therapy who was treated successfully with immunostimulating drugs.

A previously healthy 30-year old woman sustained pelvic and femur fractures, extensive soft-tissue abdominal and pelvic damage, pulmonary contusion, and second-degree burns in the terrorist bombing in Brussels in March, 2016. The patient's early hospital course was complicated by sepsis, femur osteomyelitis, and deep wound infections with multi-drug-resistant Enterobacteriaceae. On day 15 after admission to the intensive care unit, results of CT analysis showed gastric and splenic necrosis (figure); gastric biopsy results available on day 18 revealed invasive mucormycosis, and treatment was started with liposomal amphotericin B and posaconazole.

Figure: Abdominal CT scan
CT scan with contrast, showing a lack of enhancement of splenic parenchyma (S), gas in the splenic parenchyma (arrowhead), and gastric intramural gas (arrow).

On day 22, gastrectomy and splenectomy were done; pathology showed invasive mucormycosis in the stomach and spleen with extension into peritoneal and vascular structures, but additional debridement was not feasible. Because of the poor prognosis and immunosuppression, as shown by a low absolute lymphocyte count, low monocyte HLA-DR expression, and increased expression of programmed death-1 (PD-1) on T-cells (appendix), immunoadjuvant therapy with interferon-γ (Immukine, Boehringer, Brussels, Belgium; 100 μg three times weekly for five doses) was started on day 28, followed by a single 250 mg dose of nivolumab (Opdivo, BMS, Braine l'Alleud, Belgium) on day 30. Subsequent immunological examinations showed increases in absolute lymphocyte count, monocyte HLA-DR expression, and CD8 T-cells, and decreased T-cell PD-1 expression (appendix). The patient improved slowly, and repeat CT scans showed no residual infection. The patient was discharged from the intensive care unit 80 days after admission.

This patient, with well documented fungal sepsis, showed typical features of post-aggression immunosuppression involving defective innate and adaptive immunity.[1,2] Interferon-γ and the anti-PD-1 monoclonal antibody nivolumab reversed these defects. Interferon-γ restores monocyte function and has been used as rescue therapy for life-threatening fungal infections in patients not responding to conventional treatment.[3–5] Nivolumab binds to PD-1, blocks interaction with its ligands, PD-L1 and PD-L2, and releases PD-1 pathway-mediated inhibition of T-cell proliferation and cytokine production. Anti-PD-1 has shown activity in animal models of fungal sepsis and in patients with chronic hepatitis C virus infection.[4] A phase I clinical trial of nivolumab in the treatment of severe sepsis is about to begin (NCT02960854).

Combination immunotherapy has been proposed as a possible advance in sepsis treatment.[5] To our knowledge, this is the first report showing efficacy of such an approach in a patient with life-threatening fungal infection unresponsive to conventional therapy.

RSH has research support funding from Bristol Myers Squibb, the maker of nivolumab, and is also doing clinical trials with anti-PD-L1, an investigational drug made by Bristol Myers Squibb, in sepsis. All other authors declare no competing interests. The patient provided consent for publication of this letter.

*David Grimaldi, Olivier Pradier, Richard S Hotchkiss, *Jean-Louis Vincent*
jlvincent@intensive.org

Department of Intensive Care (DG, J-LV) and Department of Haematology (OP), Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; and Department of Anesthesiology and Critical Care Medicine, Washington University School of Medicine, St Louis, MO, USA (RSH)

1 Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL. Immune defense against Candida fungal infections. *Nat Rev Immunol* 2015; **15**: 630–42.
2 Kullberg BJ, van de Veerdonk F, Netea MG. Immunotherapy: a potential adjunctive treatment for fungal infection. *Curr Opin Infect Dis* 2014; **27**: 511–16.
3 Delsing CE, Gresnigt MS, Leentjens J, et al. Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series. *BMC Infect Dis* 2014; **14**: 166.
4 Attanasio J, Wherry EJ. Costimulatory and coinhibitory receptor pathways in infectious disease. *Immunity* 2016; **44**: 1052–68.
5 Hotchkiss RS, Opal S. Immunotherapy for sepsis—a new approach against an ancient foe. *N Engl J Med* 2010; **363**: 87–89.

Early ICU course
Acute Lung Injury
Osteomyelitis
Deep wound infectio
MDR enterobacteria
Mucormycosis (day 15)

Immunomonitoring (day 16)
Low levels of mHLA-DR
High levels of PD1 on T cells

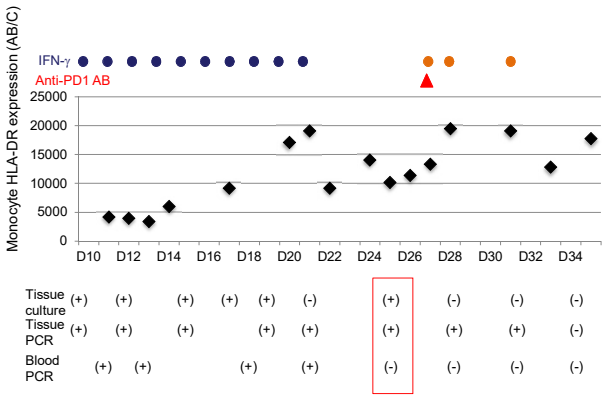
Very poor prognosis
+ immunosuppression

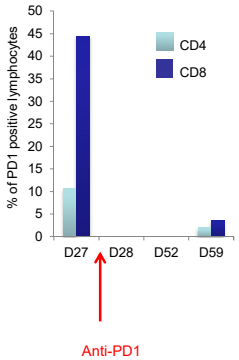
Immunkin (IFNg)
ivolumab (anti PD-1)

2017 THE LANCET Infectious Diseases

Nivolumab and Interferon-γ rescue therapy to control invasive mucormycosis after necrotising fasciitis and septic shock

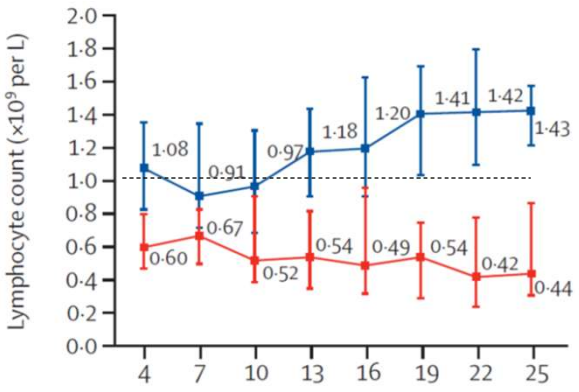
Immumonitoring showed severe lymphopenia and very low mHLA-DR expression
=> severe immunosuppression





Recent examples from COVID-19 pandemic

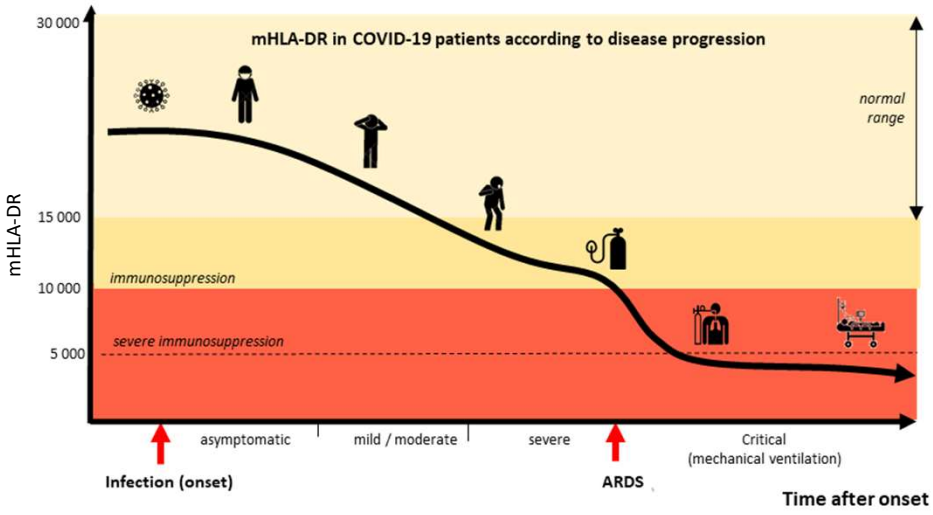
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study



THE LANCET

Zhou et al., 2020 (March)

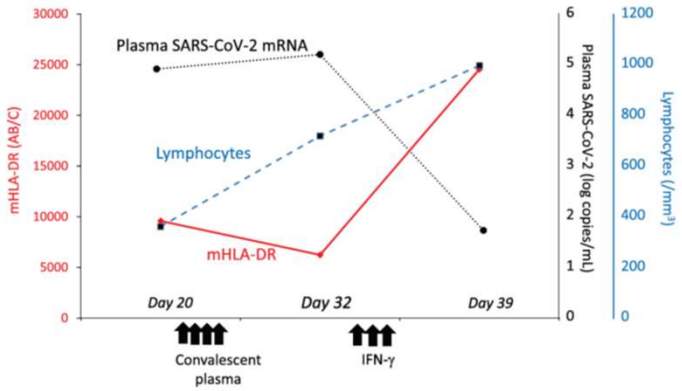
COVID-19 as a viral sepsis



Benlyamani et al., Cytometry A 2020

Clinical trials in immunostimulation = IFNγ

Immunostimulation with interferon-γ in protracted SARS-CoV-2 pneumonia

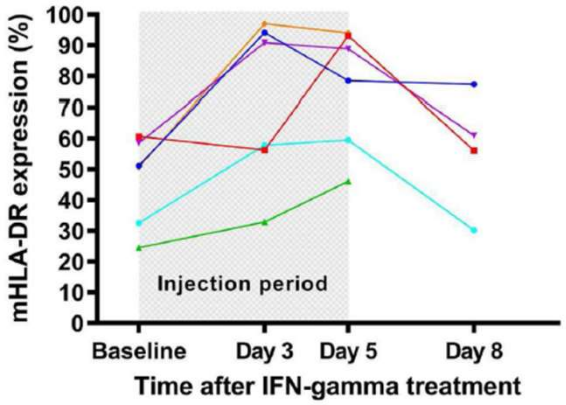


Lukaszewicz et al., 2021

JOURNAL OF MEDICAL VIROLOGY

Potential role for interferon gamma in the treatment of recurrent ventilator-acquired pneumonia in patients with COVID-19: a hypothesis

Lee S. Nguyen[1,2], Zakaria Ait Hamou[1,5], Nabil Gastli[3], Nicolas Chapuis[4,5] and Frédéric Pène[1,5*]



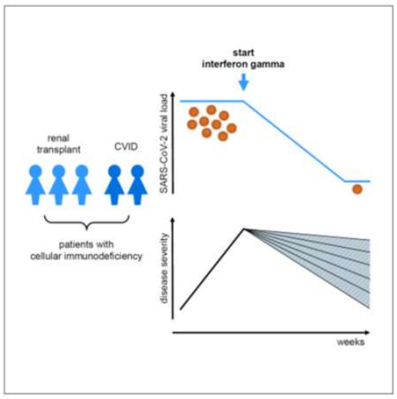
2021

Case Report

Interferon gamma immunotherapy in five critically ill COVID-19 patients with impaired cellular immunity: A case series

Med

Van Larrhoven et al., 2021



Highlights

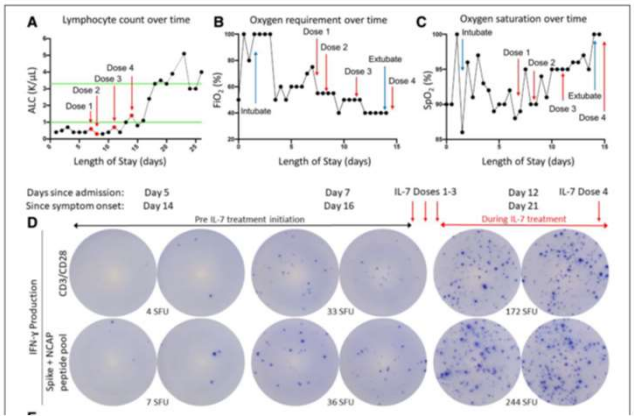
Five immunocompromised, critically ill COVID-19 patients were treated with IFN-γ

IFN-γ treatment was followed by viral clearance and clinical improvement

The patients did not develop signs of hyperinflammation

Patients on mechanical ventilator
+ Persisting viral load and no clinical improvements after > 10 days after admission

Interleukin-7 Reverses Lymphopenia and Improves T-Cell Function in Coronavirus Disease 2019 Patient With Inborn Error of Toll-Like Receptor 3: A Case Report

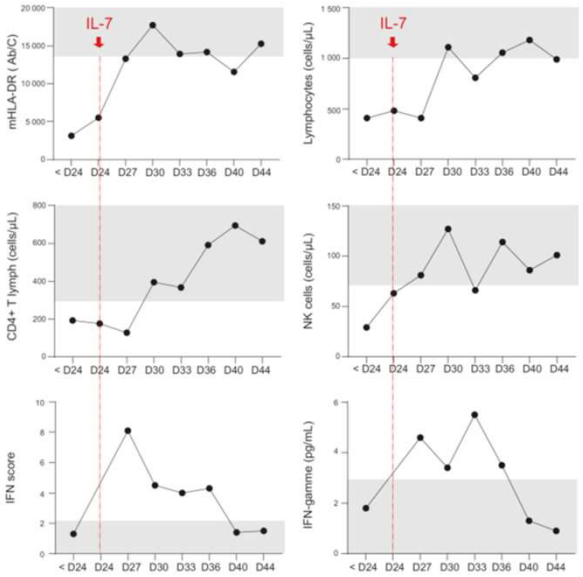


43-y-old
Worsening hypoxemia
Dexamethasone
High flow oxygen, convalescent plasma
remdisivir

Severe lymphopenia (CD4 < 500)

Mazer et al, 2021 *Critical Care Explorations*

Immune monitoring of interleukin-7 compassionate use in a critically ill COVID-19 patient



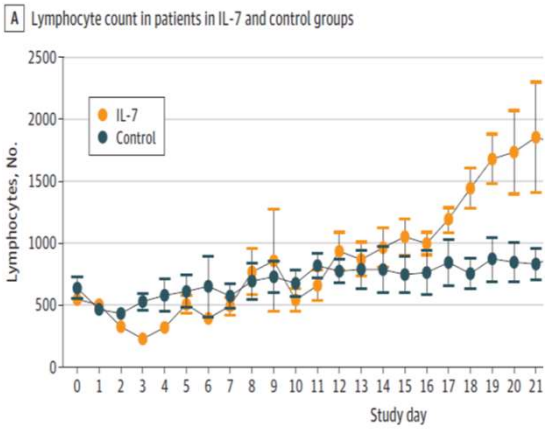
Monneret et al., 2020

Cellular & Molecular Immunology

Research Letter | Infectious Diseases

Association of Interleukin 7 Immunotherapy With Lymphocyte Counts Among Patients With Severe Coronavirus Disease 2019 (COVID-19)

Pierre Francois Laterre, MD; Bruno François, MD; Christine Collienne, MD; Philippe Hantson, MD, PhD; Robin Jeannet, PhD; Kenneth E. Remy, MD; Richard S. Hotchkiss, MD



+ Essai ILIAD (2022)

JAMA Netw Open 2020

apm news

DÉPÊCHE - Jeudi 06 janvier 2022 - 18:10

Un effort "majeur" reste à faire pour individualiser le traitement du Covid sévère

Le Pr Timsit a rappelé lors de son audition les différentes phases de la maladie: la partie virale initiale "pas très sévère", la partie immunologique qui a un effet délétère "considérable" sur l'organisme et, chez les patients les plus sévères, la phase "d'immuno-paralysie post-agressive" caractérisée par des surinfections et des complications infectieuses qui dégradent lourdement le pronostic des malades, en particulier les plus sévères.

ASSEMBLÉE NATIONALE

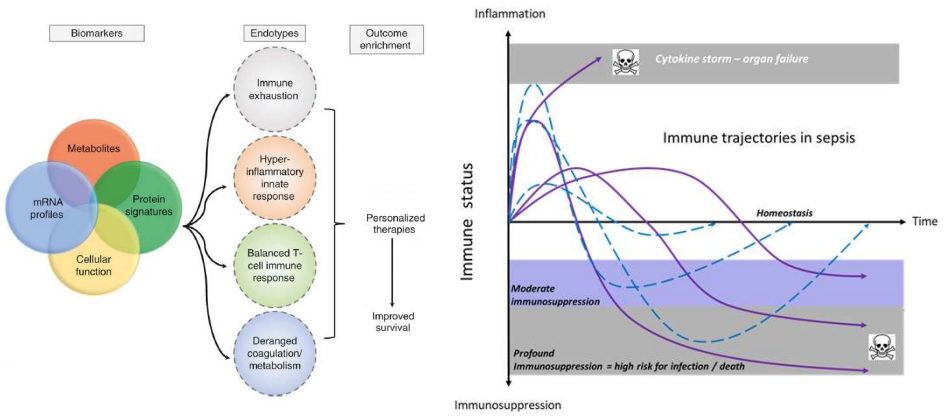
Assemblée nationale, F, 6 janvier 2022

Conclusions

Immunostimulation (summary)

- Septic ICU patients are immunosuppressed
- Immunostimulation = promising approach
- Preclinical results in sepsis : +++
- Several clinical cases and small RCT : +++
- In > 500 patients, no adverse “cytokine storm”
- Available makers for individualized therapies

...because one size does **not** fit all...

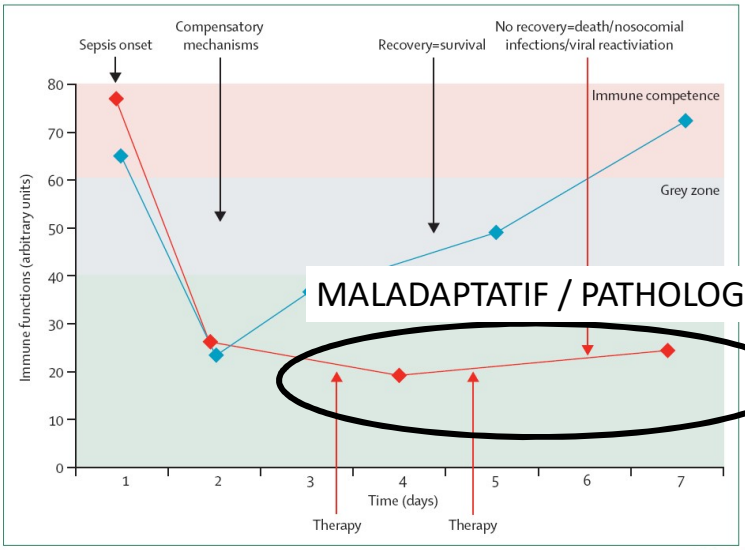


Leligdowicz and Matthay, Crit Care 2018

Monneret et al., Cytometry Part A 2019

Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach

Richard S Hotchkiss, Guillaume Monneret, Didier Payen



MALADAPTATIF / PATHOLOGIQUE

Lancet Infect Dis 2013; 13: 260–68

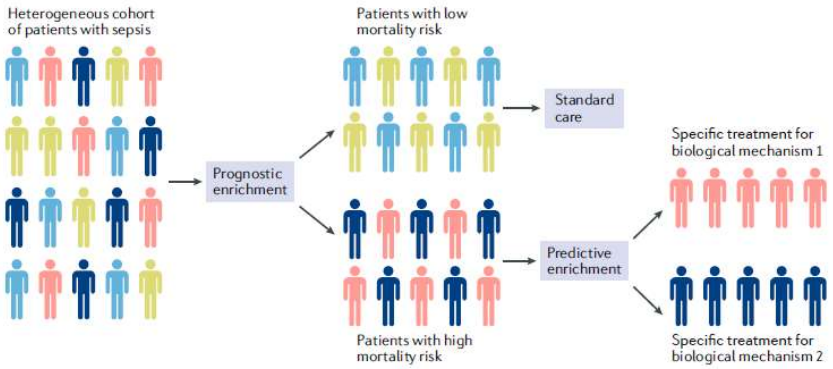
Immunodépression dans le sepsis principales caractéristiques

Immunité innée
- Neutrophiles immatures & MDSC = ↑
- % Monocyte désactivés = ↑
- Capacité présentation Ag : ↓

Immunité adaptative
- Lymphopénie
- Molécules inhibitrices PD-1 = ↑
- Répertoire Lymphocytaire : ↓

Soins courants
Immuno - HCL

Prognostic and predictive enrichment in sepsis



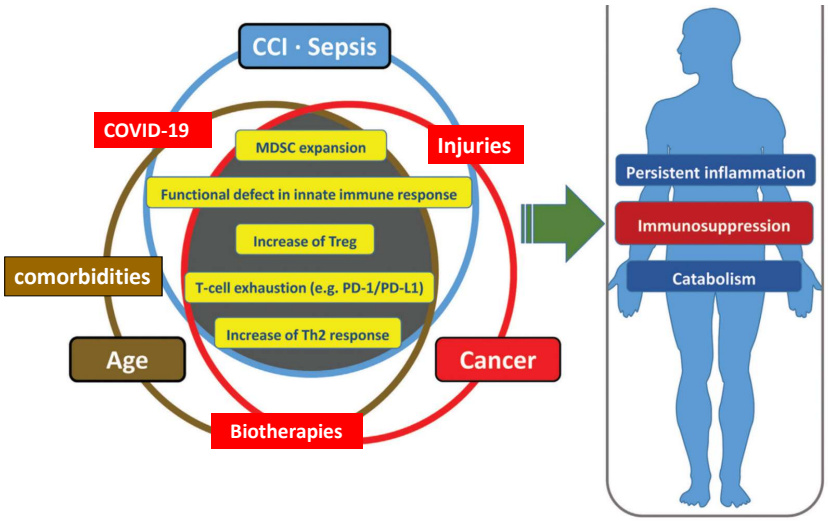
Stanski & Wong, Nat Rev Nephrol 2019

Any given life-threatening infection results, by definition, from an immunodeficiency, whether inherited or acquired

Casanova JL, Science 2007

Science AAAS

The future :
Immuno(suppression) at the crossroads of many (ICU) diseases



Adapted from Horiguchi et al., Frontiers Immunol 2018